BarTH Syndrome Symptom Assessment (BTHS-SA) – Adolescent version

Instructions: The following questions ask about **Barth Syndrome**. Please select the response that best describes your experience with Barth Syndrome **over the past 24 hours.** Please select only one answer for each question. Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

Please indicate (with a check mark ☑) responses to the questions below.

1. Please rate your worst feeling of tiredness at rest in the past 24 hours.	☐ No tiredness at all	☐ Mild tiredness	☐ Moderate tiredness	☐ Severe tiredness	☐ Very severe tiredness
2. Please rate your worst feeling of tiredness during activities in the past 24 hours.	☐ No tiredness at all	☐ Mild tiredness	☐ Moderate tiredness	☐ Severe tiredness	☐ Very severe tiredness
3. Please rate your worst feeling of muscle weakness at rest in the past 24 hours.	☐ No muscle weakness at all	☐ Mild muscle weakness	☐ Moderate muscle weakness	☐ Severe muscle weakness	☐ Very severe muscle weakness
4. Please rate your worst feeling of muscle weakness during activities in the past 24 hours.	☐ No muscle weakness at all	☐ Mild muscle weakness	☐ Moderate muscle weakness	☐ Severe muscle weakness	☐ Very severe muscle weakness
5. Please rate your worst feeling of muscle pain at rest in the past 24 hours.	☐ No muscle pain at all	☐ Mild muscle pain	☐ Moderate muscle pain	☐ Severe muscle pain	☐ Very severe muscle pain
6. Please rate your worst feeling of muscle pain due to activities in the past 24 hours.	☐ No muscle pain at all	☐ Mild muscle pain	☐ Moderate muscle pain	☐ Severe muscle pain	☐ Very severe muscle pain
7. Please rate your worst feeling of early fullness when eating in the past 24 hours.	☐ No feeling of early fullness at all	☐ Mild feeling of early fullness	☐ Moderate feeling of early fullness	☐ Severe feeling of early fullness	☐ Very severe feeling of early fullness
8. Please rate your worst difficulty eating (for example, chewing and/or swallowing) in the past 24 hours.	☐ No difficulty eating at all	☐ Mild difficulty eating	☐ Moderate difficulty eating	☐ Severe difficulty eating	☐ Very severe difficulty eating
9. Please rate your worst feeling of headache in the past 24 hours.	☐ No headache at all	☐ Mild headache	☐ Moderate headache	☐ Severe headache	☐ Very severe headache

Supplementary Figure 1. BTHS-SA measurement tool for adolescent subjects, younger than 18 years.

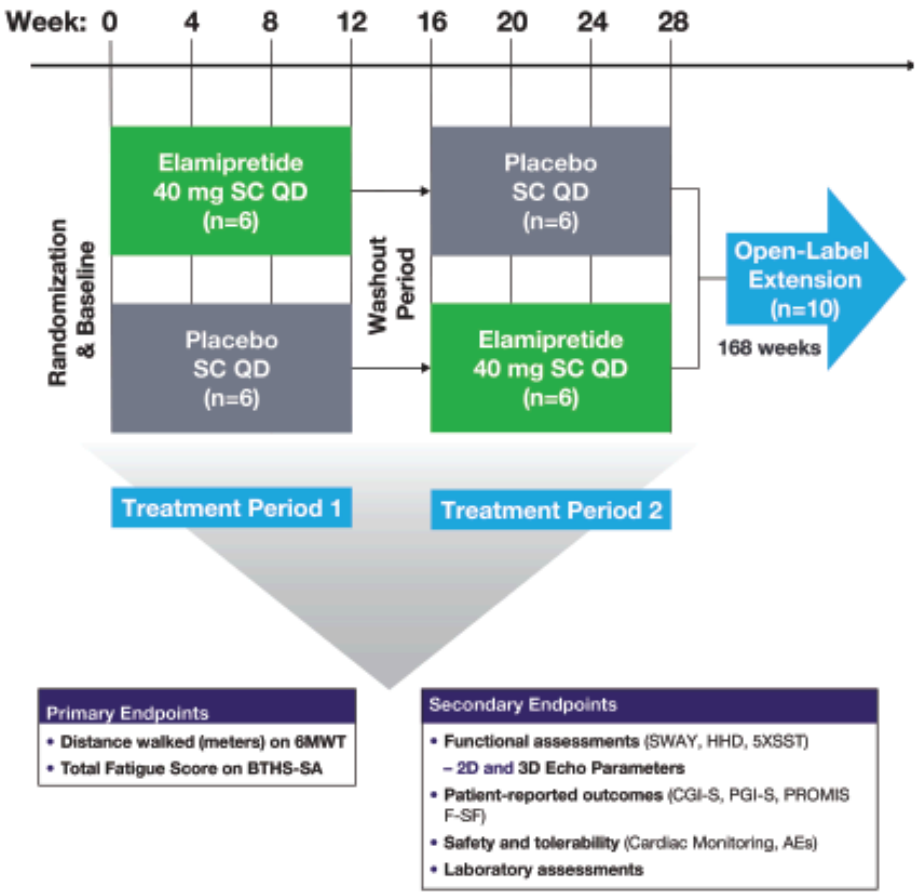
BarTH Syndrome Symptom Assessment (BTHS-SA) – Adult version

Instructions: The following questions ask about **Barth Syndrome**. Please select the response that best describes your experience with Barth Syndrome **over the past 24 hours.** Please select only one answer for each question. Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

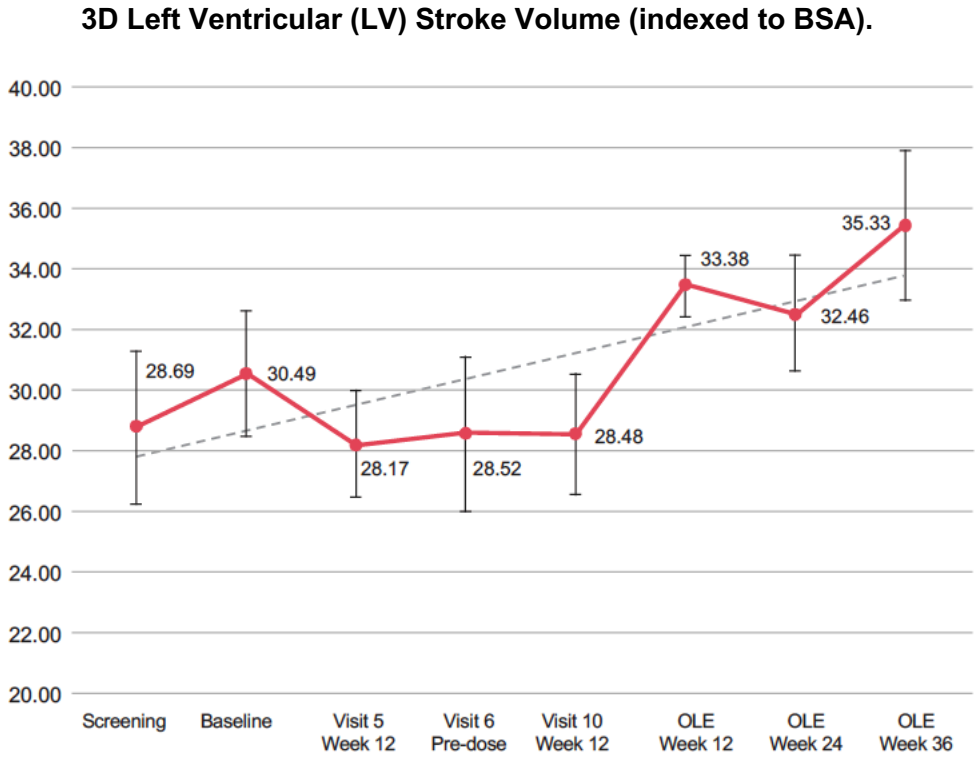
Please indicate (with a check mark ☑) responses to the questions below.

1. Please rate your worst feeling of tiredness at rest in the past 24 hours.	No tiredness at all ☐	Mild tiredness ☐	Moderate tiredness ☐	Severe tiredness ☐	Very severe tiredness ☐
2. Please rate your worst feeling of tiredness during activities in the past 24 hours.	No tiredness at all ☐	Mild tiredness ☐	Moderate tiredness ☐	Severe tiredness ☐	Very severe tiredness ☐
3. Please rate your worst feeling of muscle weakness at rest in the past 24 hours.	No muscle weakness at all ☐	Mild muscle weakness ☐	Moderate muscle weakness ☐	Severe muscle weakness ☐	Very severe muscle weakness ☐
4. Please rate your worst feeling of muscle weakness during activities in the past 24 hours.	No muscle weakness at all ☐	Mild muscle weakness ☐	Moderate muscle weakness ☐	Severe muscle weakness ☐	Very severe muscle weakness ☐
5. Please rate your worst feeling of muscle pain at rest in the past 24 hours.	No muscle pain at all ☐	Mild muscle pain ☐	Moderate muscle pain ☐	Severe muscle pain ☐	Very severe muscle pain ☐
6. Please rate your worst feeling of muscle pain due to activities in the past 24 hours.	No muscle pain at all ☐	Mild muscle pain ☐	Moderate muscle pain ☐	Severe muscle pain ☐	Very severe muscle pain ☐
7. Please rate your worst feeling of dizziness/lightheadedness in the past 24 hours.	No dizziness/ lightheaded ness at all ☐	Mild dizziness/ lightheaded ness ☐	Moderate dizziness/ lightheaded ness ☐	Severe dizziness/ lightheaded ness ☐	Very severe dizziness/ lightheaded ness ☐
8. Please rate your worst feeling of shortness of breath in the past 24 hours.	No shortness of breath at all ☐	Mild shortness of breath ☐	Moderate shortness of breath ☐	Severe shortness of breath ☐	Very severe shortness of breath ☐

Supplementary Figure 2. BTHS-SA measurement tool for adult subjects, age 18 years and older.

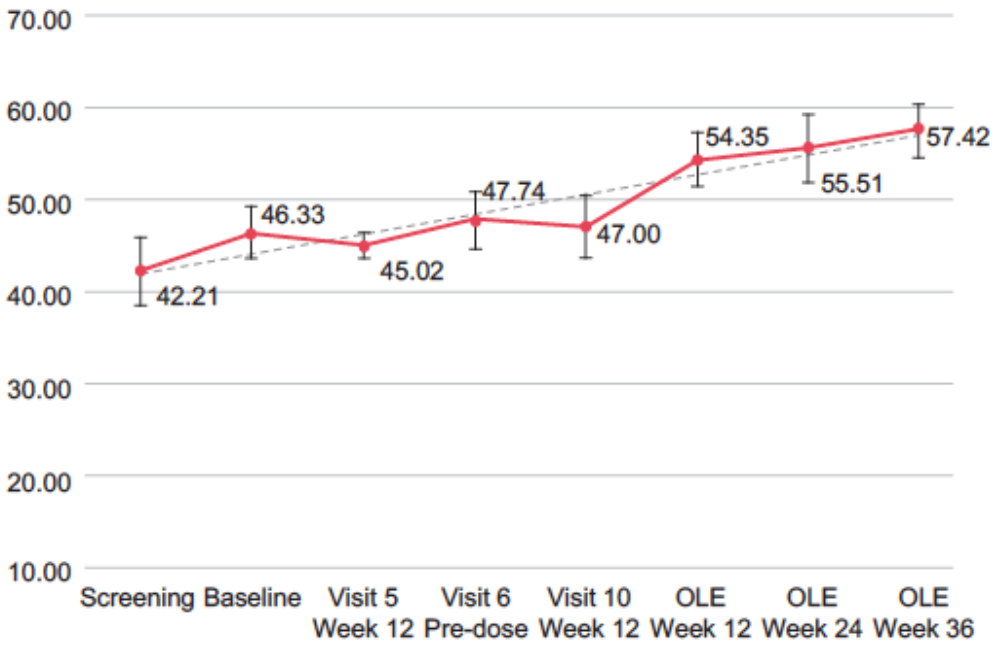


Supplementary Figure 3. Study design for SPIBA-201 to test the efficacy and safety of single daily SC doses of 40 mg elamipretide (vs placebo) in subjects with Barth Syndrome. Subjects were randomized (1:1) to one of two sequence groups: 12-weeks of single daily SC doses of 40 mg elamipretide in Treatment Period 1 followed by 12-weeks of treatment with placebo in Treatment Period 2 (separated by 4-week washout period), or vice versa.



Supplementary Appendix Figure 4. 3D Left Ventricular (LV) Stroke Volume (indexed to BSA). Utilizing a slope model of individual regression lines for each subject to determine the consistent change in indexed stroke volume over the course of exposure, there is a significant trend of an increase in stroke volume over time ($p<0.01$) For the 8 subjects who completed Week 36, Part 2mean z-scores improved from -1.38 at Baseline to -0.56 at week 36, Part 2 respectively. This corresponds to a mean stroke volume in the 20th percentile at Baseline and in the 33rd percentile at Week 36, Part 2.

Average Left Ventricular End Diastolic Volume indexed to BSA.

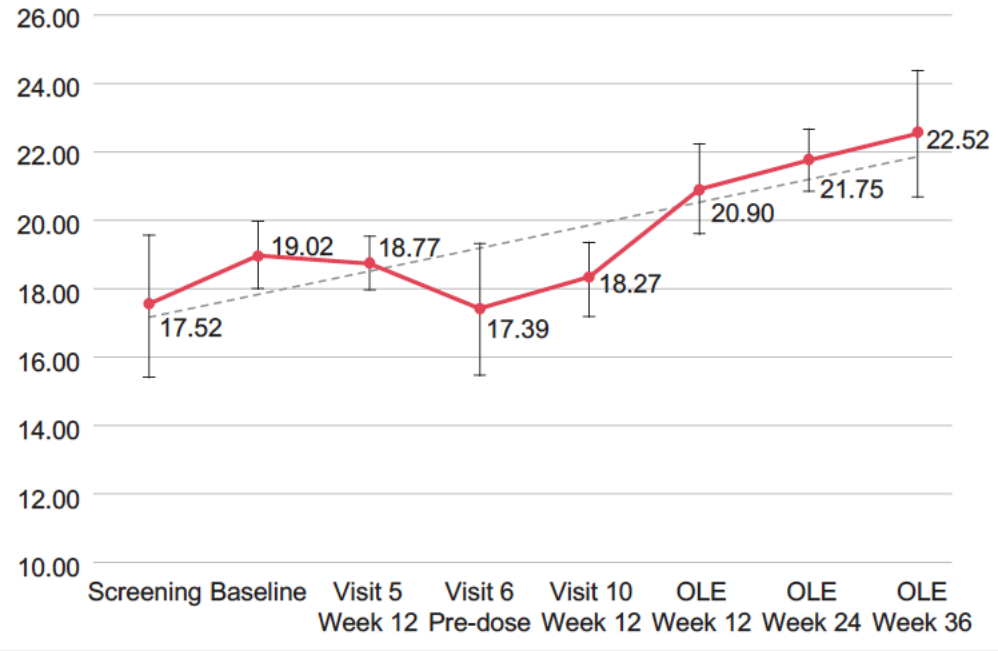


Supplementary Figure 5. Average Left Ventricular End Diastolic Volume indexed to BSA. Echocardiographic assessments revealed low Left Ventricular End Diastolic Volume (LV EDV) in all subjects. On average, LV EDV was below the 8th percentile Z-scores, which are used to express the deviation of a given measurement from the size or age specific population (Chubb et al., Ann Pediatr Cardiol. 2012). Seven subjects were at or below the 2nd percentile Z-scores on LV EDV.

Although statistically significant evidence of a carryover or sequence effect was not observed during Part 1, subjects randomized to elamipretide therapy during Treatment Period 1 of Part 1 demonstrated a greater overall improvement in LV EDV during Part 1, with a median increase of 20mL versus a median increase of 8mL for those randomized to elamipretide therapy during Treatment Period 2. Moreover, subjects randomized to elamipretide in Treatment Period 1 of Part 1 appeared to continue to experience improvement in LV EDV during Treatment Period 2 on placebo, which may be indicative of a carryover or sequence effect. This may support the premise that improvements began upon exposure to elamipretide therapy and gradually increase over time. At Week 12, Week 24, and Week 36, following open-label treatment with elamipretide, the

mean 3D LV EDV indexed to BSA were 54.35, 55.51, and 57.42 mL/m2, respectively. There were not statistically significant mean changes from baseline noted for all three visits. For the 8 patients completing Week 36, Part 2 mean z-scores improved from -1.59 to -0.79, respectively. This corresponds to a mean LV EDV in the 12th percentile at baseline and in the 27th percentile at Week 36, Part 2.

Average Left Ventricular End Systolic Volume indexed to BSA.



Supplementary Figure 6. Average Left Ventricular End Systolic Volume indexed to BSA. On average, Left Ventricular End Systolic Volume (LV ESV) was below the 8th percentile Z-scores, and six subjects were below the 2nd percentile Z-scores. At Week 12, Week 24, and Week 36, following open-label treatment with elamipretide, the mean 3D LV ESV indexed to Body Surface Area (BSA) was 20.90, 21.75, and 22.52 mL/m^2, respectively. A statistically significant mean change from baseline was observed at Week 12 ($p = 0.0349$); no statistically significant changes from baseline were noted for Week 24 and Week 36. For the 8 patients completing who completed Week 36, Part 2 mean Z-scores improved from -1.40 to -0.89, respectively. This corresponds to a mean LV ESV in the 14th percentile at baseline and in the 23rd percentile at Week 36, Part 2. Absolute

mean changes in LV ESV are shown below at Week 36 (noting for purposes of clarity that total number of subjects decreases from 12 in Part 1 to 8 by Week 36 of Part 2).

Supplementary Appendix, Table 1. TAZ variants

Subject ID	TAZ pathogenic Variant
1	c.110-2A>G
2	c.171del, p.Gly58AlafsX25
3	Ex1_Ex5del
4	c.800_818delinsGGG, p.Thr267fs*6
5	c.284+5G>A
6	Ex2_Ex5del
7	c.589G>A, p.Gly197Arg
8	c.526+2T>G
9	c.589G>A, p.Gly197Arg
10	c.589G>A, p.Gly197Arg
11	c.873_874dup, p.Arg292Leufs*49
12	c.873_874dup, p.Arg292Leufs*49

Inclusion Criteria:
A subject must meet ALL of the following Inclusion Criteria at the Baseline Visit:

1. Willing and able to provide signed informed consent form (ICF) prior to participation in any trial-related procedures. If applicable, informed consent in writing from parent(s) or legally-acceptable representative(s) and, informed assent from subject (if age appropriate according to local requirements) should be provided
2. Agrees to adhere to the trial requirements for the length of the trial
3. Genetically confirmed Barth Syndrome in the opinion of the Investigator
4. Male aged ≥ 12 years
5. At the Screening Visit, subject body weight and estimated glomerular filtration rate (eGFR) meeting one of the following:
    a. Body weight >30 kg AND eGFR ≥ 90 mL/min/1.73 m2 at the Screening visit
    b. Body weight >40 kg AND eGFR ≥ 60 mL/min/1.73 m2 at the Screening visit GFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation:
        eGFR (mL/min/1.73 m2) = 175 x (SCr*)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African American) *=serum creatinine
6. Ambulatory and impaired, in the opinion of the Investigator, during the 6-Minute Walk Test at the Baseline Visit
7. Subject has been on stable (unchanged and constant) medications (including over-the counter
treatments, vitamins, or supplements), or medications that will not impact the safety or efficacy endpoints of the trial, in the opinion of the Investigator for at least 30 days prior to the Baseline Visit
8. Male subjects with female partners of child-bearing potential must be willing to use a highly effective method of contraception from the Screening Visit through at least 2 months following the last injection

Supplementary Appendix Table 2a. SPIBA-201, Part 1 Inclusion Criteria and SPIBA-201.

Exclusion Criteria:
A subject must NOT meet any of the following exclusion criteria at the Baseline Visit:

1. Participated in another interventional clinical trial within 30 days of or is currently enrolled in a non-interventional clinical trial at the Baseline Visit judged by Investigator to be potentially confounding with the current trial
2. Any prior or current medical condition that, in the judgment of the Investigator, would prevent the subject from safely participating in and/or completing all trial requirements
3. Undergone an in-patient hospitalization within 30 days prior to the Baseline Visit or is likely to need in-patient hospitalization or surgical procedure during the course of the trial
4. Subject is undergoing an apparent pubertal growth spurt in the opinion of the Investigator
5. Subject has uncontrolled hypertension in the judgment of the Investigator (e.g. consistently elevated above >160 mmHg systolic or >100 mmHg diastolic despite appropriate treatment)
6. Subject has a history of clinically significant hypersensitivity or allergy to any of the excipients contained in the investigational medicinal product (IMP)
7. Subject has a history of active substance abuse during the year before the Baseline Visit, or is thought, for any reason, likely not to be compliant in the opinion of the Investigator
8. History of heart transplantation or current placement (or within the past year) on the waiting list for a heart transplantation
9. a. For subjects with an implantable cardioverter defibrillator (ICD): the known occurrence of ICD therapy/discharge in the 3 months prior to the Baseline Visit and/or expected to undergo re-implantation during the conduct of the study
    b. For subjects without an implantable cardioverter defibrillator (ICD): expected to undergo an implantation of an ICD during the conduct of the study
10. Currently receiving treatment with chemotherapeutic agents or immunosuppressant agents or has received prior radiation therapy to the chest
11. Recipient of stem cell or gene therapy or is currently being treated by a therapeutic investigational device

Part 2 Continuation Criteria
A subject must meet all of the following Part 2 Continuation Criteria at the Treatment Period 2 Week 12 Visit of Part 1 to be eligible for Part 2:

1. Subjects must continue to be able and willing to adhere to the trial requirements
2. Subject is appropriate to continue in Part 2 (i.e. subject was compliant in Part 1), in the opinion of the Investigator
3. Subject has not had a serious adverse event (SAE) related to the IMP
4. Subject has not permanently discontinued the IMP

Supplementary Appendix Table 2b. SPIBA-201, Part 1 Exclusion Criteria and SPIBA-201 and Part 2 Continuation Criteria.

Part 1. Primary Objective
To evaluate the effect of single daily subcutaneous (SC) doses of 40 mg elamipretide administered for 12 weeks in subjects with Barth Syndrome on the:

• Distance walked (meters) during the 6-Minute Walk Test (6MWT)
• Total Fatigue on the BarTH Syndrome Symptom Assessment (BTHS-SA)

Part 1. Secondary Objectives
To evaluate the effect of single daily SC doses of 40 mg elamipretide administered for 12 weeks in subjects with Barth Syndrome as measured by change in:

- Muscle strength as measured by handheld dynamometry (HHD)
- Five Times Sit-to-Stand Test (5XSST)
- 2-D and 3-D Echocardiographic measurements
- Accelerometry counts
- SWAY Application Balance Assessment
- Patient Reported Outcomes
- Clinician Global Impression (CGI) Scales
- Caregiver Global Impression (CaGI) Scales
- Biomarkers

To evaluate the safety and tolerability of single daily SC doses of 40 mg elamipretide administered for 12 weeks in subjects with Barth Syndrome

Part 2. Primary Objective
To assess the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide for up to 168 weeks

Part 2. Secondary Objectives
To evaluate longitudinal trends of single daily SC doses of 40 mg elamipretide administered for up to 168 weeks in subjects with Barth Syndrome as measured by:
• 6MWT
• Total Fatigue on the BTHS-SA
• Muscle strength as measured by HHD
• 5XSST
• 2-D and 3-D Echocardiographic measurements
• SWAY Application Balance Assessment
• Patient Reported Outcomes
• CGI Scales
• CaGI Scales
• Biomarkers

Supplementary Table 3. Primary and secondary outcome objectives for SPIBA-201, Part 1 and SPIBA-201, Part 2.

Characteristic	Treatment Sequence AB (N = 6)	Treatment Sequence BA (N = 6)	All Subjects (N = 12)
Age (years), n	6	6	12
Mean (SD)	23.3 (9.07)	15.7 (3.33)	19.5 (7.65)
Median	22.0	15.5	16.5
Min, Max	(14, 35)	(12, 21)	(12, 35)
Sex, n	6	6	12
Male	6 (100.0%)	6 (100.0%)	12 (100.0%)
Female	0	0	0
Race, n	6	6	12
White	6 (100.0%)	5 (83.3%)	11 (91.7%)
Multiple[1]	0	1 (16.7%)	1 (8.3%)
Ethnicity, n	6	6	12
Hispanic	0	0	0
Non-Hispanic	6 (100.0%)	6 (100.0%)	12 (100.0%)
Weight (kg), n	6	6	12
Mean (SD)	54.50 (20.768)	47.18 (18.035)	50.84 (18.934)
Median	52.95	40.20	43.75
Min, Max	(33.7, 85.9)	(31.4, 74.5)	(31.4, 85.9)
Height (cm), n	6	6	12
Mean (SD)	169.75 (16.637)	164.80 (13.195)	167.28 (14.547)
Median	171.15	163.55	167.10
Min, Max	(150.4, 187.7))	(152.0, 180.0)	(150.4, 187.7)
Body Mass Index (kg/m^2), n	6	6	12
Mean (SD)	18.23 (3.677)	16.88 (4.179)	17.56 (3.818)
Median	17.40	14.75	15.60
Min, Max	(14.9, 24.4)	(13.6, 23.0)	(13.6, 24.4)

Abbreviations: Max = Maximum; Min = Minimum; SD = standard deviation
A = Elamipretide, B = Placebo
n = number of subjects contributing to the summary statistics. Percentages were based on n for each characteristic.
1. Refers to White/American Indian or Alaska Native.

Supplementary Table 4. Summary of Demographic Characteristics enrolled in SPIBA-201 Part 1. A total of 16 subjects were screened and 12 of these subjects were randomized into Part 1 of SPIBA-201. All 12 randomized subjects completed both Treatment Periods in Part 1. Overall, the majority of subjects in Part 1 were White (91.7%), Non-Hispanic or Latino (100.0%), with a mean (SD) age of 19.5 (7.65) years. Four participants were between the ages of 12-14y11m years, 4 participants were between the ages of 15 and 19 years 11 months, 2 participants were between 20-29 years 11 months, and 2 participants were between 30-40 years of age. Mean (SD) weight and BMI were 50.84 (18.934) and 17.56 (3.818), respectively. One subject (16.7%) included in the trial was Indian or an Alaskan Native.

Demographics of each treatment sequence were generally similar to the overall population with some variability observed in overall age, age ranges, weight, and BMI. Subjects in treatment sequence AB (elamipretide-placebo) were slightly older, ranging in age between 14 and 35 years (mean (SD): 23.3 (9.07) years), while subjects in treatment sequence BA (placebo-elamipretide) were slightly younger, ranging in age between 12 and 21 years (mean (SD): 15.7 (3.33) years), compared to the overall population which ranged between 12 and 35 years. For subjects in treatment sequence AB, mean weight and BMI were 54.50 kg and 18.23 kg/m^2, respectively. Mean weight and BMI were lower for subjects in treatment sequence BA (47.18 kg and 16.88 kg/m^2, respectively).

Subject ID	1	2	3	4	5	6	7	8	9	10	11	12
3-D Echocardiogram Parameter												
LV End Diastolic Volume (mL)/BSA	-15.83	-6	0.51	11.45	35.64	23.89	6.05	2.26	7.94	11.09	4.52	5.77
LV End Systolic Volume (mL)/BSA	-3.74	-2.93	0	4.61	13.73	6.43	0.84	-0.66	3.06	3.72	4.44	1.38
LV Stroke Volume (mL)/BSA	-12.09	-3.07	0.51	6.84	21.91	17.46	5.21	2.93	4.88	7.38	0.08	4.39
2-D Echocardiogram Parameter												
LV Mass (g)/BSA	17.37	15.12	16.85	27.98	-6.04	0	-9.24	-10.49	8.74	36.02	-4.93	31.71
Peak E (m/s)/Peak A (m/s)	-0.36	-0.05	-0.42	0.04	0.55	-0.38	-1.05	-0.94	0.09	0.54	0.26	1.16
LV Global Longitudinal Strain (Triplane) (%)	-1.9	-0.5	3.7	0.1	3.4	2.1	2.7	-2.6	1.6	-1.1	2.1	0.5
Tricuspid Regurgitation (semi-quant.)	Trivial → None	Mild → None	Trivial → Trivial	Trivial → None	Trivial → Trivial	Trivial → None	Trivial → Trival	Trivial → None	Trivial → None	None → None	Mild → Mild	Mild → Mild
Chin:Ratio (X/Y) at LV Apex at End-Diastole	0.1	0.13	0.1	-0.05	0.01	0.07	-0.06	0	0.04	0.02	0.08	0.17
Jenni:Ratio (NC/C) at LV Apex at End-Systole	-0.4	-0.2	0.08	-0.22	0.12	-0.3	-0.25	0.2	0.01	-1.34	-0.13	-0.1

Supplementary Table 5. Full profile of echocardiographic changes from SPIBA-201, Part 1 Baseline to SPIBA-201, Part 2, Week 36. 3-D echocardiogram parameters highlighted in green indicate improvement from baseline.

	Elamipretide 40 mg (N = 12)		Placebo (N = 12)	
	n (%)	Number of Events	n (%)	Number of Events
At least one TEAE	12 (100.0)	74	10 (83.3)	47
TEAEs related to study treatment	12 (100.0)	48	8 (66.7)	13
SAEs	0	0	0	0
SAEs related to study treatment[1]	0	0	0	0
TEAEs leading to discontinuation of study treatment	0	0	0	0
Death	0	0	0	0

Abbreviations: AE = Adverse event; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event
Percentages are based on N.
An AE is considered treatment-emergent if the date of onset is on or after the date of the first dose of study treatment and is associated with the treatment most recently received by the subject at the time of onset or worsening.
Any AE with an onset during the washout period will be attributed to treatment in Treatment Period 1.
1. Related = probably related or possibly related to study treatment.

Supplementary Table 6. **SPIBA-201, Part 1 Treatment emergent adverse events**. There were 121 reported treatment emergent adverse events (TEAE); 74 events were reported in the elamipretide group and 47 events were reported in the placebo group. TEAEs occurred more often in subjects when receiving 40 mg elamipretide (48 events in 12 [100.0%] subjects) compared to when receiving placebo (13 events in 8 [66.7%] subjects); however, all of the treatment-related TEAEs on elamipretide are injection site related. The most common TEAE overall was injection site erythema, followed by injection site pain, with higher incidence of subjects treated with elamipretide (100.0% and 75.0%, respectively) compared to placebo (25.0% and 33.3%, respectively). The majority of TEAEs were mild or moderate in severity. There were more TEAEs that were moderate in severity in subjects treated with elamipretide (6 [50.0%] subjects), than with placebo (1 [8.0%] subjects). There were no subjects with severe TEAEs reported. There were no deaths, severe adverse events (SAEs), or TEAEs leading to discontinuation during Part 1 of the trial.

	Total Events, N (%)	Mild	Moderate	Severe
	N (%)	N (%)	N (%)	N (%)
At least one TEAE	**10 (100.0)**	**1 (10.0)**	**8 (80.0)**	**1 (10.0)**
General disorders and administration site conditions	**10 (100.0)**	**7 (70.0)**	**3 (30.0)**	**0**
Injection site erythema	8 (80.0)			
Injection site pain	7 (70.0)			
Injection site pruritus	7 (70.0)			
Nervous system disorders	**6 (60.0)**	**3 (30.0)**	**3 (30.0)**	**0**
Dizziness	4 (40.0)			
Injury, poisoning, and procedural complications	**4 (40.0)**	**1 (10.0)**	**2 (20.0)**	**1 (10.0)**
Joint dislocation	2 (20.0)			
Respiratory, thoracic and mediastinal disorders	**3 (30.0)**	**1 (10.0)**	**2 (20.0)**	**0**
Oropharyngeal pain	2 (20.0)			

Supplementary Table 7. Severity of treatment emergent adverse events in Part 2 (Open Label Extension). The most common TEAE overall was injection site erythema, followed by injection site pain. The majority of TEAEs were mild or moderate in severity.

CLINICAL TRIAL PROTOCOL

A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF SUBCUTANEOUS INJECTIONS OF ELAMIPRETIDE (MTP-131) IN SUBJECTS WITH GENETICALLY CONFIRMED BARTH SYNDROME FOLLOWED BY AN OPEN-LABEL TREATMENT EXTENSION

Trial Phase:	Phase 2
Trial Number:	SPIBA-201
Document Version:	Version 4.0
Final Approval Date:	15 March 2018
Sponsor:	Stealth BioTherapeutics, Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466 United States of America
Sponsor Chief Clinical Development Officer:	Chief Clinical Development Officer
Sponsor Medical Monitor:	Medical Monitor

PROTOCOL APPROVAL

Protocol Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Crossover Trial to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneous Injections of Elamipretide (MTP-131) in Subjects with Genetically Confirmed Barth Syndrome Followed by an Open-Label Treatment Extension
Protocol Number:	SPIBA-201
Protocol Date:	15 March 2018

Signatures electronically applied. See last page of file for signature certificate/date

Date

Chief Clinical Development Officer
Stealth BioTherapeutics, Inc.

1. SYNOPSIS

Name of Sponsor/Company: Stealth BioTherapeutics, Inc.

Investigational Product: Elamipretide (MTP-131)

Title of Trial: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Crossover Trial to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneous Injections of Elamipretide (MTP-131) in Subjects with Genetically Confirmed Barth Syndrome Followed by an Open-Label Treatment Extension

Objectives: This trial is designed with 2 parts, SPIBA-201 (Part 1) and SPIBA-201 OLE (Part 2). The objectives of each part are consistent with the trial design.

- Part 1 is a 28-week, randomized, double-blind, placebo-controlled crossover assessment of the efficacy and safety of single daily subcutaneous (SC) doses of 40 mg elamipretide (vs placebo) as a treatment for subjects with Barth Syndrome.
- Part 2 is an up to 168-week, open-label assessment of the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide in subjects with Barth Syndrome.

Part 1 objectives are:

Primary

- To evaluate the effect of single daily subcutaneous (SC) doses of 40 mg elamipretide administered for 12 weeks in subjects with Barth Syndrome on:
  - Distance walked (meters) during the 6-Minute Walk Test (6MWT)
  - Total Fatigue on the BarTH Syndrome Symptom Assessment (BTHS-SA)

Secondary

- To evaluate the effect of single daily SC doses of 40 mg elamipretide administered for 12 weeks in subjects with Barth Syndrome as measured by change in:
  - Muscle strength as measured by handheld dynamometry (HHD)
  - Five Times Sit-to-Stand Test (5XSST)
  - 2-D and 3-D Echocardiographic measurements
  - Accelerometry counts
  - SWAY Application Balance Assessment
  - Patient Reported Outcomes
  - Clinician Global Impression (CGI) Scales
  - Caregiver Global Impression (CaGI) Scales
  - Biomarkers

- To evaluate the safety and tolerability of single daily SC doses of 40 mg elamipretide administered for 12 weeks in subjects with Barth Syndrome

Part 2 objectives are:

Primary

- To assess the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide for up to 168 weeks

Secondary

- To evaluate longitudinal trends of single daily SC doses of 40 mg elamipretide administered for up to 168 weeks in subjects with Barth Syndrome as measured by:
  - 6MWT
  - Total Fatigue on the BTHS-SA
  - Muscle strength as measured by HHD
  - 5XSST
  - 2-D and 3-D Echocardiographic measurements
  - SWAY Application Balance Assessment
  - Patient Reported Outcomes
  - CGI Scales
  - CaGI Scales
  - Biomarkers

Pharmacokinetic (PK)

- To assess PK via a population model

Methodology:

This randomized, double-blind, placebo-controlled crossover trial followed by an open-label treatment extension assessment will enroll approximately 12 subjects who have genetically confirmed Barth Syndrome. There are 2 parts to this trial.

- Part 1 is a 28-week, randomized, double-blind, placebo-controlled crossover assessment of the efficacy and safety of single daily SC doses of 40 mg elamipretide (vs placebo) in subjects with Barth Syndrome. Subjects will be randomized (in a ratio of 1:1) to one of two sequence groups:

  – 12-weeks of single daily subcutaneous (SC) doses of 40 mg elamipretide in Treatment Period 1 followed by 12-weeks of treatment with placebo in Treatment Period 2 (separated by 4-week washout period)

  – 12-weeks of single daily subcutaneous (SC) doses of placebo in Treatment Period 1 followed by 12-weeks of treatment with 40 mg elamipretide in Treatment Period 2 (separated by 4-week washout period)

- Part 2 is an up to 168-week, open-label assessment of the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide in subjects with Barth

Syndrome. Subjects who continue into Part 2 will receive treatment with 40 mg SC elamipretide for up to 168 weeks.

Note that the duration of Part 2 treatment for each subject will be the shortest of the following:

- 168 weeks
- Regulatory approval and commercial availability of elamipretide
- Termination of the clinical development for elamipretide in subjects with Barth Syndrome.

Part 1

This randomized, double-blind, placebo-controlled crossover trial will enroll approximately 12 subjects who have genetically confirmed Barth Syndrome. Subjects will be randomized (1:1) to one of two sequence groups: 12-weeks of single daily subcutaneous (SC) doses of 40 mg elamipretide in Treatment Period 1 followed by 12-weeks of treatment with placebo in Treatment Period 2 (separated by 4-week washout period), or vice versa. The Part 1 Trial Schematic is presented in Attachment 3.

Screening Period: The Screening Period will begin with the signature of the informed consent form (ICF) and will last for at least 7 days and no more than 28 days and will include a Screening Visit. During the Screening Period, subjects will undergo all screening procedures as described in the Part 1 Schedule of Assessment (Attachment 1) including applying and wearing the AVIVO™ MPM System daily for approximately 7 consecutive days and completing the age appropriate BarTH Syndrome Symptom Assessment (BTHS-SA) daily. Confirmation of Barth Syndrome will incorporate a review of the Investigator submitted diagnosis and genetic results. Confirmation of Barth Syndrome must be made prior to randomizing the subject. Subjects who complete all screening procedures during the Screening Period and continue to meet all trial requirements, including all inclusion and none of the exclusion criteria, will be randomized and enter Treatment Period 1.

Treatment Period 1: Treatment Period 1 will begin on the day of Treatment Period 1 Baseline (Pre-dose) Visit, which is defined as Treatment Period 1 Day 1. At the Treatment Period 1 Baseline Visit, following completion of all Baseline procedures described in the Trial Schedule, the subject will be administered investigational medicinal product (IMP) (elamipretide or placebo) subcutaneously at the trial center. The Investigator (or designee) will also place a new AVIVO™ MPM System on the subject's chest and instruct the subject to continue to wear the System for approximately 7 consecutive days. At the discretion of the Investigator, the subject may return to the trial center on Treatment Period 1 Days 2 through 5 to receive a daily subcutaneous injection of the IMP. At the Treatment Period 1 Baseline Visit, subjects (and caregivers) will be trained on the procedure for self-administration of IMP. The IMP should be administered at approximately the same time each day (e.g. early morning, noon, early afternoon, or evening). The Visiting Nurse will complete assessments at the Treatment Period 1 Week 1, 4, and 8 Nurse Visits as described in the Schedule of Visiting Nurse Assessments (Attachment 2). The trial center and Visiting Nurse will remind subjects to complete the age appropriate BTHS-SA daily throughout Treatment Period 1 and to apply and wear a new AVIVO™ MPM System daily for approximately 7 consecutive days immediately prior to the Treatment Period 1 Week 12 Visit. Treatment Period 1 will conclude with the Treatment Period 1 Week 12 visit at the trial center where the subjects will return all used

vials, unused vials, and used AVIVO™ MPM Systems to the trial center.
Washout Period: The Washout will begin after the Treatment Period 1 Week 12 Visit and will last for at least 28 days (+7 days). During the Washout Period, subjects will continue to follow all trial requirements, including completing the age appropriate BTHS-SA daily.
Treatment Period 2: Treatment Period 2 will begin on the day of Treatment Period 2 Pre-dose Visit, which is defined as Treatment Period 2 Day 1. At the Treatment Period 2 Pre-dose Visit, following completion of all Pre-dose procedures described in the Trial Schedule, the subject will be administered IMP subcutaneously at the trial center. The Investigator (or designee) will also place a new AVIVO™ MPM System on the subject's chest and instruct the subject to continue to wear the System for approximately 7 consecutive days. At the discretion of the Investigator, the subject may return to the trial center on Treatment Period 2 Days 2 through 5 to receive a daily subcutaneous injection of IMP. The IMP should be administered at approximately the same time each day (e.g. early morning, noon, early afternoon, or evening). The Visiting Nurse will complete assessments at the Treatment Period 2 Week 1, 4, and 8 Nurse Visits as described in the Schedule of Visiting Nurse Assessments (Attachment 2). The trial center and Visiting Nurse will remind subjects to complete the age appropriate BTHS-SA daily throughout Treatment Period 2 and to apply and wear a new AVIVO™ MPM System daily for approximately 7 consecutive days immediately prior to the Treatment Period 2 Week 12 Visit. Treatment Period 2 will conclude with the Treatment Period 2 Week 12 visit at the trial center where the subjects will return all used vials, unused vials, and used AVIVO™ MPM Systems to the trial center.
Part 1 Follow-Up Period: At the Treatment Period 2 Week 12 Visit, the subject and the Investigator will determine whether the subject will continue into Part 2 (confirming the subject meeting the Continuation Criteria). Subjects who will not continue into Part 2 will complete the Part 1 Follow-Up Period and Part 1 End-of-Trial Visit. The Part 1 Follow-Up Period will begin after completion of Treatment Period 2 Week 12 and will last for 28 days (+7 days). During the Part 1 Follow-Up Period, subjects will continue to follow all trial requirements, including completing the age appropriate BTHS-SA daily. At the end of the Part 1 Follow-Up Period, subjects will return to the trial center for the Part 1 End-of-Trial/Early Discontinuation Visit for final safety and efficacy assessments as described in the Trial Schedule, and to return all trial materials/equipment

For Part 1, an external Data and Safety Monitoring Board (DSMB) will be established to review safety data on a regular basis to ensure safety of all subjects enrolled.

Part 2
While there is no screening period for Part 2, subjects must meet the Part 2 Continuation Criteria. Subjects who decide not to continue to Part 2 at the Treatment Period 2 Week 12 Visit of Part 1 are not eligible to participate in Part 2. The Part 2 Schedule of Assessments is provided in Attachment 1. The Part 2 Trial Schematic is presented in Attachment 3.
Part 2 Treatment Period: The Part 2 Treatment Period will begin on the day after the Treatment Period 2 Week 12 Visit of Part 1. Subjects (or trained caregivers) will administer the IMP daily during the Part 2 Treatment Period. The subject will return to the clinical site for the Part 2 Week 12, 24, 36, 48, 72, 96, 120, 144, 168 Visits for assessments, to administer the IMP (subject or trained caregiver), and to return all used IMP supplies. Phone calls (or other forms of communication) will be made to the subject every 12 weeks between clinical site visits (i.e.

weeks 60, 84, 108, 132, 156). During the Treatment Period, subjects will continue to follow all trial requirements.
Subjects who withdraw consent or are withdrawn from the trial by the investigator should be encouraged to complete an Early Discontinuation Visit as soon as possible and an effort should be made to complete and report the assessments as thoroughly as possible up to the date of withdrawal.
Part 2 Follow-Up Period: The Part 2 Follow-Up Period will begin after completion of the Part 2 Week 168 Visit and will last for 4 weeks. Subjects will continue to follow all trial requirements. Subjects will return to the clinical site for the Part 2 End-of-Trial Visit for final safety assessments, as described in the Part 2 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

Number of Subjects (planned): Approximately 12 subjects will be randomized 1:1 to one of two sequence groups, to receive subcutaneous placebo then subcutaneous elamipretide, or vice-versa, in this 2-period cross-over trial followed by an open-label treatment extension assessment.

Investigational Product, Dosage and Mode of Administration
Elamipretide (MTP-131) will be supplied as a sterile solution for subcutaneous injection. The dose of elamipretide will be 40 mg administered as a once daily SC injection. Additional details regarding the IMP will be provided in the Pharmacy Manual. IMP should be administered by either a trained caregiver or the subject via daily SC injection in the abdomen (rotating around the four abdominal quadrants) or thigh, provided that it is at least 5 cm from the previous day's location of administration, at approximately the same time each day (e.g. early morning, noon, early afternoon, or evening).

Reference Product: The placebo for this trial will be composed of the excipients used to manufacture the investigational drug but without the active drug substance. The placebo will be handled and administered identically to active drug.

Inclusion Criteria:

A subject must meet ALL of the following Inclusion Criteria at the Baseline Visit:

1. Willing and able to provide signed informed consent form (ICF) prior to participation in any trial-related procedures. If applicable, informed consent in writing from parent(s) or legally-acceptable representative(s) and, informed assent from subject (if age appropriate according to local requirements) should be provided
2. Agrees to adhere to the trial requirements for the length of the trial
3. Genetically confirmed Barth Syndrome in the opinion of the Investigator
4. Male aged ≥ 12 years
5. At the Screening Visit, subject body weight and estimated glomerular filtration rate (eGFR) meeting one of the following:
    a. Body weight >30 kg AND eGFR ≥ 90 mL/min/1.73 m^2 at the Screening visit
    b. Body weight >40 kg AND eGFR ≥ 60 mL/min/1.73 m^2 at the Screening visit

eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation:

eGFR (mL/min/1.73 m^2) = 175 x (SCr*)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African American) *=serum creatinine

6. Ambulatory and impaired, in the opinion of the Investigator, during the 6-Minute Walk Test at the Baseline Visit
7. Subject has been on stable (unchanged and constant) medications (including over-the-counter treatments, vitamins, or supplements), or medications that will not impact the safety or efficacy endpoints of the trial, in the opinion of the Investigator for at least 30 days prior to the Baseline Visit
8. Male subjects with female partners of child-bearing potential must be willing to use a highly effective method of contraception (see Section 9.11.1 for details) from the Screening Visit through at least 2 months following the last injection

Exclusion Criteria:

A subject must NOT meet any of the following exclusion criteria at the Baseline Visit:

1. Participated in another interventional clinical trial within 30 days of or is currently enrolled in a non-interventional clinical trial at the Baseline Visit judged by Investigator to be potentially confounding with the current trial
2. Any prior or current medical condition that, in the judgment of the Investigator, would prevent the subject from safely participating in and/or completing all trial requirements
3. Undergone an in-patient hospitalization within 30 days prior to the Baseline Visit or is likely to need in-patient hospitalization or surgical procedure during the course of the trial
4. Subject is undergoing an apparent pubertal growth spurt in the opinion of the Investigator
5. Subject has uncontrolled hypertension in the judgment of the Investigator (e.g. consistently elevated above >160 mmHg systolic or >100 mmHg diastolic despite appropriate treatment)
6. Subject has a history of clinically significant hypersensitivity or allergy to any of the excipients contained in the investigational medicinal product (IMP)
7. Subject has a history of active substance abuse during the year before the Baseline Visit, or is thought, for any reason, likely not to be compliant in the opinion of the Investigator
8. History of heart transplantation or current placement (or within the past year) on the waiting list for a heart transplantation
9. a. For subjects with an implantable cardioverter defibrillator (ICD): the known occurrence of ICD therapy/discharge in the 3 months prior to the Baseline Visit and/or expected to undergo re-implantation during the conduct of the study
   b. For subjects without an implantable cardioverter defibrillator (ICD): expected to undergo an implantation of an ICD during the conduct of the study
10. Currently receiving treatment with chemotherapeutic agents or immunosuppressant agents or has received prior radiation therapy to the chest
11. Recipient of stem cell or gene therapy or is currently being treated by a therapeutic investigational device

Part 2 Continuation Criteria

A subject must meet all of the following Part 2 Continuation Criteria at the Treatment Period 2 Week 12 Visit of Part 1 to be eligible for Part 2:

1. Subjects must continue to be able and willing to adhere to the trial requirements
2. Subject is appropriate to continue in Part 2 (i.e. subject was compliant in Part 1), in the opinion of the Investigator
3. Subject has not had a serious adverse event (SAE) related to the IMP
4. Subject has not permanently discontinued the IMP

Planned Trial Duration: Up to 204 weeks

This trial is designed with 2 parts, Part 1 and Part 2.

Part 1: Up to 32 weeks (up to 36 weeks if not continuing into Part 2)

Screening: At least 7 days and no more than 28 days
Treatment Period 1: 12 weeks
Washout: 4 weeks
Treatment Period 2: 12 weeks
Part 1 Follow-Up: 4 weeks (for subjects not continuing into Part 2).

Part 2: Up to 172 weeks

Part 2 Treatment Period: 168 weeks
Part 2 Follow-Up: 4 weeks

Criteria for Evaluation:

Primary Endpoints

- Distance walked (meters) during the 6-Minute Walk Test (6MWT)
- Total Fatigue on the BTHS-SA

Secondary Endpoints

- Muscle strength as measured by handheld dynamometry (HHD)
- Five Times Sit-to-Stand Test score
- 2-D and 3-D Echocardiographic measurements
- Accelerometry counts
- SWAY Application Balance Assessment
- Patient reported outcomes
    - PROMIS Short Form Fatigue
    - Fatigue During Activities on the BTHS-SA
    - Patient Global Impression (PGI) Scales
        - PGI of Symptoms
        - PGI of Change
    - EQ-5D
- Clinician Global Impression (CGI) Scales
    - CGI of Symptoms
    - CGI of Change

- Caregiver Global Impression (CaGI) Scales
  - CaGI of Symptoms
  - CaGI of Change
- Biomarkers
  - MLCL: L4-CL Ratio
  - Plasma and blood biomarkers (GDF-15, FGF-21, glutathione/reduced glutathione)
  - Urine biomarkers (8-isoprostane,8-hydroxy-2-deoxyguanosine, 3-methylgutaconic acid)
  - Plasma and urine metabolomics
  - Exploratory biomarkers
- Adverse Events (AEs)
- Vital signs
- Electrocardiograms (ECGs)
- Ambulatory arrhythmias
- Clinical laboratory evaluations
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Pharmacokinetic (PK) Endpoints

- Assessment of PK via a population model

Statistical Methods:

Analysis Populations

Safety Population: All subjects who receive at least 1 dose of IMP, according to the treatment received.

Intention-to-Treat (ITT) Population: All subjects who receive at least 1 dose of IMP will be included, according to the treatment sequence group to which they were randomized.

Per-Protocol (PP) Population: Includes all ITT subjects without major protocol violations/deviations. The list of major protocol violations/deviations will be identified and specified prior to final database lock for the trial that would lead to exclusion for the PP analysis.

Pharmacokinetic (PK) Population: Includes all trial subjects who have at least 1 PK sample taken during their participation.

Safety Analyses

Safety analyses will include incidence of AEs and SAEs, deaths, premature discontinuation from the trial due to an AE (regardless of relationship to IMP), and change in ECG, clinical laboratory data, and vital signs.

Efficacy Analyses

Efficacy analyses will be conducted on the ITT population. In general, categorical variables will be summarized by the count (N) and percentage of subjects (%). Continuous variables will be summarized by the number of non-missing observations (N), mean, standard deviation, median, minimum, and maximum values. All trial data are to be displayed in the data listings.

Subject disposition summaries will include the number of subjects enrolled and the numbers included in the ITT populations. The number and percentage of subjects who complete or discontinue from the trial will be summarized by reason for discontinuation.

Subject's age, sex, weight, height, body mass index (BMI), and other demographic characteristics will be recorded and summarized. Medical history will be listed.
Two primary endpoints are included in the primary endpoint family (6MWT and BTHS-SA - Total Fatigue). Hochberg's procedure will be used to control the family-wise Type I error rate at 0.05 (two-sided). No adjustments will be made to alpha levels to account for secondary efficacy measures. Statistical analysis of this trial will be the responsibility of the Sponsor or its designee.
Additional details regarding analyses will be included in separate statistical analysis plan (SAP).

Sample Size

For this Phase 2, randomized, double-blind, placebo-controlled crossover trial followed by an open-label treatment extension assessment, a sample size of approximately 12 subjects is planned. Assuming an underlying standard deviation of paired differences of 50 meters for the 6MWT distance and 1.3 points for the BTHS-SA Total Fatigue score12 subjects provides for nearly 80% power to detect a mean improvement of 50 meters in the 6MWT or 1.3 points for the BTHS-SA Total Fatigue score, with each potentially tested at the 0.025 (two-sided) level of significance (associated with a potential adjustment via Hochberg's procedure), in Part 1. Subject numbers are restricted by feasibility considerations (availability of subjects) but that recruitment could be greater if subjects are available (up to 16 subjects).

2. TABLE OF CONTENTS

3. ABBREVIATIONS AND DEFINITIONS

Term	Definition
5XSST	5X Sit to Stand Test
6MWT	6-Minute Walk Test
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration versus time curve
$AUC_{0-\tau}$	Area under the plasma concentration vs time curve from time 0 to end of the dosing interval
AUC_{0-inf}	Area under the plasma concentration curve from baseline to infinity
AUC_{0-24}	Area under the plasma concentration curve from baseline to 24 hours postdose
BTHS-SA	BarTH Syndrome Symptom Assessment
BMI	Body mass index
CaGI	Caregiver Global Impression Scales
CIOMS	Council for International Organizations of Medical Sciences
CGI	Clinician Global Impression Scales
C_{max}	Maximum plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic data capture
EF	Ejection fraction
ETC	Electron Transport Chain
FGF-21	Fibroblast Growth Factor 21
GCP	Good Clinical Practice
GDF-15	Growth Differentiation Factor 15
HHD	handheld dynamometry
IB	Investigator's Brochure

Term	Definition
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMM	Inner mitochondrial membrane
IMP	Investigational medicinal product
ISR	Injection site reaction
IV	Intravenous
ITT	Intention-to-treat
L4-CL	Tetralinoleyl-cardiolipin
LV	Left ventricular
MFD	Maximum feasible dose
mL	Milliliter
MLCL	Monolyso-cardiolipin
MTP-131	SS-31, elamipretide, or Bendavia™
mtDNA	Mitochondrial DNA
nDNA	Nuclear DNA
OLE	Open-label extension
PGI	Patient Global Impression Scales
PK	Pharmacokinetic(s)
PMM	Primary mitochondrial myopathy
PT	Preferred term
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

4. INTRODUCTION

This trial will be conducted in strict accordance with the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, ICH GCP guidelines, and all applicable laws and regulations. For detailed information on the investigational medicinal product (IMP) and the nonclinical and clinical studies conducted to date, please refer to the most recent edition of the elamipretide Investigator's Brochure (IB).

4.1. Barth Syndrome

Barth Syndrome (BTHS, 3-methylglutaconic aciduria type II, MIM 300394) is a rare X-linked disorder with an estimated prevalence of 1/300,000–400,000 live births and characterized by cardiomyopathy, skeletal myopathy, neutropenia, and growth abnormalities, among other features (Ades L, et al., 1993). BTHS is caused by defects in *TAZ* (G4.5), which encodes for Tafazzin, an acyltransferase involved in the remodeling of the mitochondrial phospholipid cardiolipin. Cardiolipin has important roles in mitochondrial function including maintaining cristae structure, supporting electron transport chain efficiency, and in apoptosis. (Hoch F., 1992). Deficiency of tafazzin results in abnormal cardiolipin content, a reduction of structurally mature tetralinoleyl-cardiolipin (L4-CL) and an increase in structurally immature monolyso-cardiolipin (MLCL) (Vreken P, et al., 2000). Alterations in cardiolipin structure, content, and acyl chain composition are associated with mitochondrial dysfunction (Paradies G, et al., 2014). This dysfunction results in reduced function and efficiency of the electron transport chain (ETC), affecting oxidative phosphorylation (OXPHOS) and results in reduced ATP and likely increased reactive oxygen species (ROS) production. Presumably, disorganized oxidative phosphorylation and other aspects of mitochondrial dysfunction lead to signs and symptoms of disease.

The diagnosis of BTHS is suggested by typical clinical findings and an increase (5- to 20-fold) in urinary 3-methylglutaconic acid (3-MGC) and other urinary metabolites. The diagnosis is established via detection of a *TAZ* pathogenic variant on molecular genetic testing and/or a diagnostic assay measuring the elevation of the MLCL to L4-CL ratio (MLCL/L4-CL), which is both a highly sensitive and specific diagnostic measurement in bloodspots, nucleated cells, and tissues (Clark S, et al., 2013; Sandlers Y, et al., 2016).

BTHS is a complex inborn error of metabolism and affects many systems of the body (Jefferies J., 2013). Though not always present, cardinal characteristics of this multi-system disorder often include combinations and varying degrees of:

- Cardiomyopathy (usually dilated cardiomyopathy [DCM] with undulating hypertrophic cardiomyopathy [HCM], sometimes with left ventricular noncompaction [LVNC] and/or endocardial fibroelastosis [EFE]). This can result in ventricular arrhythmias/sudden cardiac death (SCD)
- Skeletal muscle myopathy (usually proximal myopathy, low muscle mass, and muscle weakness) resulting in exercise intolerance due to extreme fatigue
- Growth delay (short stature in the early years, followed by accelerated growth in mid- to late puberty)

- Neutropenia (can be chronic, intermittent, cyclic, or not present) resulting in life-threatening bacterial infections
- Feeding problems (e.g., difficulty sucking, swallowing, or chewing; aversion to some food textures; selective or picky eating; frequent vomiting)
- Biochemical abnormalities (cardiolipin composition abnormalities and variable 3-methylglutaconic aciduria and 3-methylglutaconic acidemia)

No treatment is approved for the treatment of individuals with BTHS

4.2. Pharmacologic Basis for Elamipretide as a Potential Treatment for BTHS

As previously described, alterations in cardiolipin structure, content, and acyl chain composition are associated with mitochondrial dysfunction (Paradies G, et al., 2014). This dysfunction results in reduced function and efficiency of the electron transport chain (ETC), affecting oxidative phosphorylation (OXPHOS) and results in reduced ATP and likely increased reactive oxygen species (ROS) production. This increase in ROS may reach a threshold and trigger additional increased ROS generation by the ETC, an effect termed "ROS-induced ROS release (RIRR)" (Zorov, D. et al., 2000; Zorov, D, et al., 2006). These effects constitute a positive feedback mechanism for enhanced ROS production leading to potentially additional significant mitochondrial structural abnormalities, dysfunction and cellular injury. At a certain level of mitochondrial dysfunction (decreased ATP and increased ROS productions), patients experience signs and symptoms of their disease.

Reactive Oxygen Species also attack and denature a number of components within the mitochondria, including the protein components of the ETC, membrane lipids (particularly cardiolipin), and mtDNA. In particular, the denaturing of cardiolipin has been associated with abnormal morphology of the inner mitochondrial membrane (IMM), less association of the ETC complexes within that membrane, a decline in activity of the ETC (ATP production), and the release of cytochrome c which initiates apoptotic signaling (Fry, M, et al., 1981; Chicco A, et al., 2007).

Studies of BTHS patient tissues and animal models of *TAZ* depletion have reported structurally abnormal mitochondria with inefficient oxidative phosphorylation, resulting in decreased ATP and increased ROS levels (Saric A, et al., 2015). Elamipretide may help to stabilize the limited number of mature L4-CL and allow them to function properly, rather than becoming dysfunctional due to being preferentially targeted by the higher levels of ROS that BTHS patients have due to the dysfunctional mitochondria. The association of elamipretide with cardiolipin has been shown to normalize key cardiolipin properties that are modified during oxidative stress. The proposed interaction of elamipretide with the limited mature cardiolipin that exists in patients with BTHS may preserve the optimal interaction of the protein complexes of the ETC, improve electron flow, increase ATP production, and decrease ROS generation.

4.3. Elamipretide Risk/Benefit Assessment

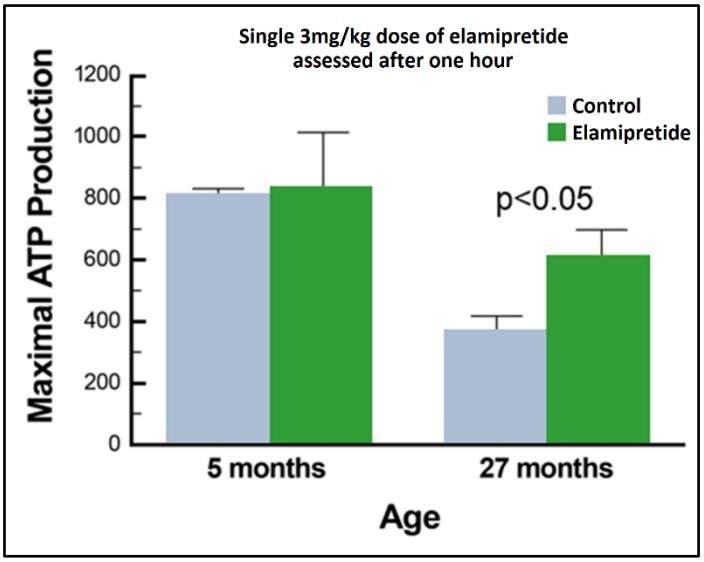
4.3.1. Potential Benefits

4.3.1.1. Pre-clinical studies

4.3.1.1.1. *Skeletal and cardiac muscle dysfunction of aged mice*

Elamipretide has been shown to be effective in restoring ATP production in preclinical models of both skeletal and cardiac muscle dysfunction of aged mice (Siegel M, et al., 2013). In this study, skeletal muscle energetics were measured *in vivo* one hour after injection of either elamipretide or saline using a combination of optical and 31P magnetic resonance spectroscopy in old and young mice (27 months and 5 months, respectively). ATP production in the old mice was found to increase and to be comparable to that in young mice one hour after a single treatment with elamipretide (Figure 1). These findings demonstrated a rapid reversal of age-related declines in resting and maximal mitochondrial ATP production, whereas, there was no observable effect on young, healthy muscle. In the same study, consistent results were observed after a week of dosing with elamipretide, with a favorable difference in the exercise tolerance of old mice, and again no significant effect was seen in young mice.

Figure 1: ATP Production in Young (5 month) and Old (27 month) Mice Following a Single Treatment with Elamipretide



Mean +/- SEM, n = 5 – 7 per group

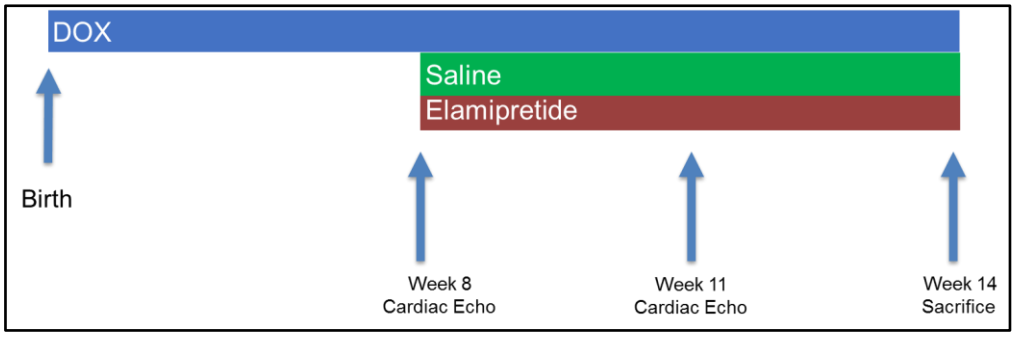
Several reports demonstrate elamipretide's ability to prevent skeletal muscle atrophy. For example, in a rat model of muscle wasting, elamipretide reduced the loss of the diaphragm muscle function caused by 12 hours of mechanical ventilation (Powers S, et al., 2011). Similarly, elamipretide prevented casting-induced (i.e., immobilization) skeletal muscle atrophy via protecting mitochondrial function (Talbert E, et al., 2013).

Additionally, in a study using a mouse model, myopathy induced by the chemotherapeutic agent doxorubicin, which induced muscle atrophy, it was shown that elamipretide protected both skeletal and heart muscle atrophy via prevention of mitochondrial ROS dysfunction and myopathy production and is, therefore, suggesting its therapeutic potential in this setting of myopathy (Min K, et al., 2011).

4.3.1.1.2. *Cardiac muscle dysfunction of tafazzin (TAZ) knockdown (TAZKD) mice*

A pre-clinical mouse model of Barth Syndrome has been used to assess potential side effects and efficacy of elamipretide (Soustek, M. S., et al. 2010). Upon induction of the TAZ-specific shRNA *in vivo* by doxycycline, TAZ mRNA levels in transgenic mice are reduced by >89% in cardiac and skeletal muscle. At week 8, elamipretide (5 mg/kg/day) or saline is administered via Alzet minipump for a period of 6 weeks. Cardiac echocardiograms are performed at weeks 8 (prior to treatment), week 11 (3 weeks treatment) and week 14 (6 weeks treatment) (Figure 2).

Figure 2: Study Schedule of Events



At week 14, the animals are sacrificed. The TAZKD mice had a 90% reduction in cardiolipin and approximately 10-fold increase in MLCL. Treatment with elamipretide did not alter this distribution. Importantly, favorable findings regarding heart function, including improvements in fractional shortening (Figure 3), and histology (ventricle diameter and degree of fibrosis) were initially observed (Figure 4). These changes were not significant across the full cohort due to variability resulting from sex and genotype (hetero vs. homozygotes), and point to the difficulty in developing an animal model for Barth which will allow efficient and timely testing of compounds.

Figure 3: Mean Fractional Shortening (FS)

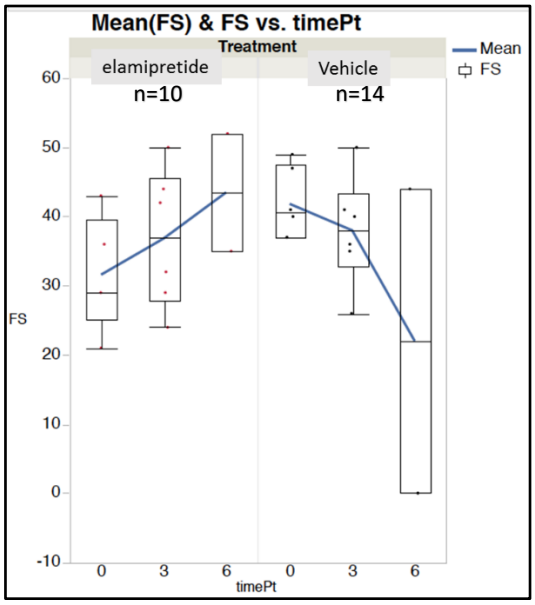
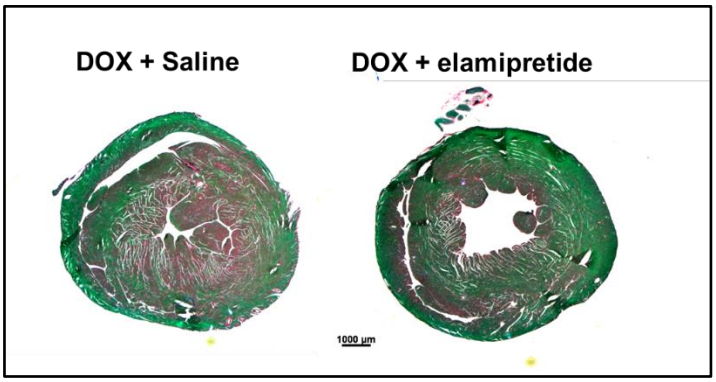


Figure 4: Picosirius Red Staining for Fibrosis of a Section of Left Ventricle



4.3.1.2. Clinical Studies in Other Genetically Confirmed Mitochondrial Diseases

No previous studies have been conducted with elamipretide in subjects with Barth Syndrome.

The SPIMM-201 trial was a phase 1/2 multi-center, randomized, double-blind, placebo-controlled, multiple ascending IV dose trial that enrolled subjects ≥16 and ≤65 years with primary mitochondrial myopathy (PMM). Three escalating doses (0.01, 0.10, and 0.25 mg/kg/hour infused for 2 hours) were studied (one dose per cohort) and infused daily for 5 days. The primary efficacy endpoint was distance walked during the 6MWT after 5 days of treatment.

Five days of daily IV elamipretide was well tolerated with no increase in adverse events or laboratory abnormalities compared to placebo. The most common TEAE overall was headache in 6 (16.7%) subjects, followed by dizziness in 3 subjects. There were no treatment-related TEAEs that were severe in intensity.

The primary efficacy measure of interest was the change from Baseline in distance walked (meters) on the 6-minute walk test (6MWT). In addition to the 6MWT, the efficacy of elamipretide was explored using Cardiopulmonary Exercise Testing (CPET) parameters, patient reported outcomes (Newcastle Mitochondrial Disease Adult Scale [NMDAS] and a Daily Symptom Questionnaire [DSQ]), and plasma and urinary biomarkers.

The highest dose of elamipretide examined in this trial, 0.25 mg/kg/hr, was associated with improvement in skeletal muscle function compared to placebo, as measured by the 6MWT (Table 1).

Table 1: Summary of Change from Baseline on Days 5 and 7 in Distance Walked (meters) on 6MWT

	Elamipretide			Placebo (N = 9)
	0.01 mg/kg/hr (N = 9)	0.10 mg/kg/hr (N = 9)	0.25 mg/kg/hr (N = 9)	
Baseline				
Mean (SD)[2]	363.9 (143.15)	421.9 (66.85)	360.2 (100.99)	369.8 (96.82)
Change on Day 5[1]				
Mean (SD)	14.2 (49.40)	34.3 (43.46)	65.4 (45.71)	20.9 (45.18)
LS Mean	13.5	36.5	64.5	20.4
LSM Diff[2] (90% CI)[3]	-7.0 (-44.1, 30.1)	16.1 (-21.6, 53.8)	44.1 (7.0, 81.2)	
p-value[3]	0.7523	0.4746	0.0528	
Change on Day 7[1]				
Mean (SD)	31.8 (41.10)	35.1 (56.56)	63.6 (63.30)	39.4 (60.74)
LS Mean	30.3	39.5	61.7	38.5
LSM Diff[2] (90% CI)[3]	-8.3 (-53.0, 36.5)	1.0 (-44.5, 46.4)	23.1 (-21.6, 67.9)	
p-value[3]	0.7561	0.9718	0.3872	

Abbreviations: 6MWT = 6-minute walk test; CI = Confidence interval; LS = Least squares; LSM Diff = Least Squares Mean Difference; SD = Standard deviation.

1. Change from Baseline = value at Visit – value at Baseline Visit.
2. LSM Difference is elamipretide dose (0.01, 0.10, or 0.25 mg/kg/hr) minus placebo.
3. P-value and 90% CI of the difference are based on the ANCOVA model which included treatment as a factor and Baseline measure as a covariate.

Additionally, there was a positive dose response with increasing dose of elamipretide as indicated in the linear trend test (p=0.014 on Day 5).

In a post-hoc analysis which adjusted for sex and baseline disease walked, allowing magnitude of treatment benefit to be related to baseline, subjects treated with the highest dose of elamipretide walked an adjusted mean (i.e., LS mean) distance of 48 meter further on Day 5, than subjects in the placebo group in the 6MWT compared to their Baseline assessment (p=0.03) (Table 2).

Table 2: Summary of Change from Baseline in Distance Walked (meters) in the 6MWT at Day 5 – Using Backward Elimination (ITT Population)

	Elamipretide			
	0.01 mg/kg/hr (N = 9)	**0.10 mg/kg/hr (N = 9)**	**0.25 mg/kg/hr (N = 9)**	**Placebo (N = 9)**
Baseline				
Mean (SD)	363.9 (143.15)	421.9 (66.85)	360.2 (100.99)	369.8 (96.82)
Change on Day 5[1]				
Mean (SD)	14.2 (49.40)	34.3 (43.46)	65.4 (45.71)	20.9 (45.18)
LS Mean	3.1	28.3	51.2	3.0
LSM Diff[2] (90% CI)[3]	0.1 (-34.9, 35.1)	25.2 (-12.9, 63.4)	48.2 (12.5, 84.0)	
p-value[3]	0.9967	0.2702	0.0297	

Abbreviations: 6MWT = 6-minute walk test; CI = Confidence interval; LS = Least squares; LSM Diff = Least Squares Mean Difference; SD = Standard deviation.

1. Change from Baseline = value at visit – value at baseline visit.
2. LSM Difference is elamipretide dose (0.01, 0.10, or 0.25 mg/kg/hr) minus placebo.
3. Based on the ANCOVA model with treatment, baseline 6MWT, baseline 6MWT-by-treatment interaction, screening 6MWT, sex baseline height, baseline weight, and randomization cohort included in the model. Backward elimination was used to include only factors with Significance Level to Stay (SLS) <=0.1 in the final ANCOVA model and presented in this table. Final Model for Day 5 included Baseline 6MWT, treatment, baseline 6MWT-by-treatment interaction, and sex.

Subgroup analysis of the 6MWT suggest that elamipretide is more effective in subjects with greater impairment at Screening, as those who initially walked <350 meter showed greater improvement following treatment compared to those who initially walked ≥350 meter.

CPET was used to assess skeletal muscle function. For all treatment groups, including placebo, there was an increase in aerobic capacity (peak VO_2 max) and a decrease in ventilatory efficiency (peak VE/VCO_2 slope). No CPET parameters were significantly different than placebo for any dose of elamipretide. Adjusted mean modified NMDAS total scores for current function and current clinical assessment did not change over time. Changes in biomarker data (plasma glutathione, plasma FGF-21, urine 8-isoprostane, and urine 8-hydroxy-2-deoxyguanosine) were not significantly different than placebo. Pharmacokinetics of elamipretide were unchanged from normal subjects in this patient population.

4.3.2. Potential Risks

4.3.2.1. Nonclinical Study Safety Findings

The nonclinical testing of elamipretide encompasses a program of studies in pharmacology, metabolism, pharmacokinetics (PK), and toxicology.

Elamipretide was effective in multiple models of cardio-renal disease and skeletal muscle dysfunction and has been active across all species tested to date, including rat, guinea pig, rabbit, dog, sheep, and pig. The effective dose range was 0.05 to 0.5 mg/kg/day. Based on

results from a battery of secondary and safety pharmacology studies, elamipretide is not expected to cause any adverse off-target pharmacodynamic effects at therapeutic concentrations.

Elamipretide did not cause end-organ toxicity at any dosage tested in either rats or dogs. Systemic toxicity at high doses was manifested primarily by acute and transient clinical signs, which are mediated by histaminergic-like reactions. Effects were associated with maximum elamipretide plasma concentration (C_{max}) and were rapidly reversible as plasma concentrations of elamipretide (and histamine) decreased. Dose administration was not associated with any adverse effects on cardiovascular, respiratory or central nervous system function; off-target non-adverse effects were limited to transient decrease of blood pressure and heart rate, consistent with histaminergic-like reactions. In all studies, the severity of the effects was proportional to C_{max} for elamipretide; thus, the safety margin is estimated based on C_{max}, and not area under the plasma-concentration-time curve (AUC). The plasma elamipretide threshold concentration for clinically-relevant adverse effects appears to be ~20,000 ng/mL in both rats and dogs, which is more than 10-fold higher than the maximum observed human exposures at clinical doses.

Intravenous administration of elamipretide to rats and dogs was well tolerated at the administration site. Local injection site reactions evident upon SC administration varied with species, dose and dose concentration.

Elamipretide was negative for genotoxicity in the full battery of tests and caused no significant hemolysis or inhibition of receptor binding. Elamipretide did result in the release of histamine from rat mast cells at a concentrations ≥ 390 µg/mL. Elamipretide was not associated with adverse effects on fertility or embryo-fetal development.

Elamipretide is metabolized via sequential C-terminal degradation to the tripeptide M1 and the dipeptide M2. The apparent t½ of M1 was comparable to that of elamipretide, whereas t½ of M2 was longer than that of elamipretide. No sex difference was evident for either metabolite. The two metabolites were evaluated for systemic toxicity and *in vivo* genotoxicity. When tested directly, both M1 and M2 were negative for gene mutation, for receptor binding, and rat mast cell degranulation. Systemic exposure to the metabolites in rats and dogs was not related to any toxicity in acute, subchronic, or chronic studies. Neither M1 nor M2 metabolites showed biological activity when evaluated in an *ex vivo* guinea pig heart model. At a concentration of 1 µM, neither metabolite provided myocardial protection against ischemic reperfusion injury.

4.3.2.2. Human Safety

Parenteral administration of elamipretide was assessed following single and multiple IV and SC doses in approximately 230 healthy subjects in 12 completed clinical pharmacology studies with data available. Single IV doses ranged from 0.005 mg/kg/hour to 0.25 mg/kg/hr, and were typically administered over 4 hours. Multiple-dose regimens ranged from 0.25 mg/kg/hr administered over 1 hour daily for 7 days to 140 mg administered over 1 hour daily for 5 days. Single SC doses ranged from 2 mg to 80 mg and were administered as 0.5 or 1 mL injections, while multiple-dose regimens of 6 mg to 80 mg were administered as 0.25, 0.5, or 1 mL injections daily for 7 days.

No safety concerns have been identified with administration of IV or SC elamipretide for up to seven days in these studies. The only systemic adverse event reported in over 5% of subjects was headache (8.8%). Nausea (2.6%), hyponatraemia (2.6%), and dizziness (2.2%) were also reported. All other events were reported with incidence of <2.0%. The majority of TEAEs were assessed by the investigator to be of mild severity, resolved without sequelae and did not require intervention. There were no significant findings for group mean clinical laboratory, vital sign, electrocardiogram (ECG), or physical examination parameters within or across trials.

The SC formulation of elamipretide has been studied in both single- and multiple-dose trials in healthy volunteers and patient populations. Generally, injection of SC elamipretide resulted in mild or moderate injection site reactions (ISRs), frequently characterized by erythema, induration, bruising, pruritus, pain, and/or urticaria. Injection site reactions were reported intermittently across dosing with elamipretide, with most subjects experiencing ISRs beginning upon first administration of elamipretide and continuing throughout treatment, with resolution of the ISRs typically occurring the day of last elamipretide administration. The resolution of ISRs, however, has occurred as late as 14 days after the end of elamipretide treatment in one subject.

In subjects with renal impairment, exposure to elamipretide and both of its metabolites (M1 and M2), as measured by AUC, increased proportionally to the degree of renal impairment. However, there was no evidence of increased toxicity as a consequence of impaired renal function. Similarly, in the drug-drug interaction studies carried out to date, co-administration of elamipretide with aspirin, with clopidogrel, or with unfractionated heparin did not indicate a change in the nature, severity or frequency of AEs to the safety profile of either elamipretide or the comparator.

Elamipretide, administered by parenteral routes, was also assessed in completed studies in multiple patient populations including subjects with stable chronic heart failure, subjects with acute coronary syndrome who were undergoing primary percutaneous coronary intervention and stenting for ST-elevation myocardial infarction, subjects with acute kidney injury undergoing percutaneous transluminal renal angioplasty, subjects with PMM, subjects over 60 years of age with evidence of skeletal muscle mitochondrial dysfunction, and in ongoing open-label studies of in subjects with PMM and age-related macular degeneration. Single and multiple IV and SC doses of elamipretide were assessed with generally no notable differences between the elamipretide and placebo arms in the frequency or severity of adverse events, except for ISRs with SC elamipretide administration. Additionally, mild eosinophilia was reported as an adverse event in numerous subjects. Laboratory data demonstrated elevations (>0.45 cells $x10^9$/L) in eosinophils beginning at approximately 3-4 weeks after initiation of elamipretide treatment in a majority of subjects. These laboratory findings have not been reported to be associated with any systemic clinical manifestations of eosinophilia. In general, these elevations appear to trend downward after longer duration of treatment (16 weeks) and were demonstrated to have returned to within normal range or to baseline levels at the follow-up visit (up to 28 days after the end of elamipretide treatment). There were no other identified safety concerns in these trials with respect to other clinical laboratory results, physical examinations, vital signs, ECG data between the elamipretide and placebo. In general, the safety profile of systemic elamipretide was consistent with the pre-existing, comorbid medical conditions.

Across all studies, both IV and SC formulations, there have been no reported pregnancies, no exposures during lactation, no overdoses, and no abuses or misuses reported

4.3.3. Conclusions

In summary, based on the clinical and nonclinical study data, acceptable safety risks are expected for the proposed current trial. Subjects will have an opportunity to report any safety concerns; hence the benefit:risk ratio of this trial is considered favorable.

5. OBJECTIVES

This trial is designed with 2 parts, SPIBA-201 (Part 1) and SPIBA-201 OLE (Part 2). The objectives of each part are consistent with the trial design.

- Part 1 is a 28-week, randomized, double-blind, placebo-controlled crossover assessment of the efficacy and safety of single daily subcutaneous (SC) doses of 40 mg elamipretide (vs placebo) as a treatment for subjects with Barth Syndrome.
- Part 2 is an up to 168-week, open-label assessment of the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide in subjects with Barth Syndrome.

5.1. Part 1 Objectives

5.1.1. Primary Objective

To evaluate the effect of single daily subcutaneous (SC) doses of 40 mg elamipretide administered for 12 weeks in subjects with Barth Syndrome on the:

- Distance walked (meters) during the 6-Minute Walk Test (6MWT)
- Total Fatigue on the BarTH Syndrome Symptom Assessment (BTHS-SA)

5.1.2. Secondary Objectives

- To evaluate the effect of single daily SC doses of 40 mg elamipretide administered for 12 weeks in subjects with Barth Syndrome as measured by change in:
    - Muscle strength as measured by handheld dynamometry (HHD)
    - Five Times Sit-to-Stand Test (5XSST)
    - 2-D and 3-D Echocardiographic measurements
    - Accelerometry counts
    - SWAY Application Balance Assessment
    - Patient Reported Outcomes
    - Clinician Global Impression (CGI) Scales
    - Caregiver Global Impression (CaGI) Scales
    - Biomarkers
- To evaluate the safety and tolerability of single daily SC doses of 40 mg elamipretide administered for 12 weeks in subjects with Barth Syndrome

5.2. Part 2 Objectives

5.2.1. Primary Objective

To assess the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide for up to 168 weeks

5.2.2. Secondary Objectives

To evaluate longitudinal trends of single daily SC doses of 40 mg elamipretide administered for up to 168 weeks in subjects with Barth Syndrome as measured by:

- 6MWT
- Total Fatigue on the BTHS-SA
- Muscle strength as measured by HHD
- 5XSST
- 2-D and 3-D Echocardiographic measurements
- SWAY Application Balance Assessment
- Patient Reported Outcomes
- CGI Scales
- CaGI Scales
- Biomarkers

5.2.3. Pharmacokinetics (PK)

- To assess PK via a population model

6. INVESTIGATIONAL PLAN

6.1. Trial Design

This randomized, double-blind, placebo-controlled crossover trial followed by an open-label treatment extension assessment will enroll approximately 12 subjects who have genetically confirmed Barth Syndrome. There are 2 parts to this trial.

- Part 1 is a 28-week, randomized, double-blind, placebo-controlled crossover assessment of the efficacy and safety of single daily SC doses of 40 mg elamipretide (vs placebo) in subjects with Barth Syndrome. Subjects will be randomized (in a ratio of 1:1) to one of two sequence groups:
    - 12-weeks of single daily subcutaneous (SC) doses of 40 mg elamipretide in Treatment Period 1 followed by 12-weeks of treatment with placebo in Treatment Period 2 (separated by 4-week washout period)
    - 12-weeks of single daily subcutaneous (SC) doses of placebo in Treatment Period 1 followed by 12-weeks of treatment with 40 mg elamipretide in Treatment Period 2 (separated by 4-week washout period)
- Part 2 is an up to 168-week, open-label assessment of the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide in subjects with Barth Syndrome. Subjects who continue into Part 2 will receive treatment with 40 mg SC elamipretide for up to 168 weeks.

  Note that the duration of Part 2 treatment for each subject will be the shortest of the following:
    - 168 weeks
    - Regulatory approval and commercial availability of elamipretide
    - Termination of the clinical development for elamipretide in subjects with Barth Syndrome.

6.1.1. Part 1

This randomized, double-blind, placebo-controlled crossover trial will enroll approximately 12 subjects who have genetically confirmed Barth Syndrome. Subjects will be randomized (1:1) to one of two sequence groups: 12-weeks of single daily subcutaneous (SC) doses of 40 mg elamipretide in Treatment Period 1 followed by 12-weeks of treatment with placebo in Treatment Period 2 (separated by 4-week washout period), or vice versa. The Part 1 Trial Schematic is presented in Attachment 3.

Screening Period: The Screening Period will begin with the signature of the informed consent form (ICF) and will last for at least 7 days and no more than 28 days and will include a Screening Visit. During the Screening Period, subjects will undergo all screening procedures as described in the Part 1 Schedule of Assessments (Attachment 1) including applying and wearing the AVIVO™ MPM System daily for approximately 7 consecutive days and completing the age appropriate BarTH Syndrome Symptom Assessment (BTHS-SA) daily.

Confirmation of Barth Syndrome will incorporate a review of the Investigator submitted diagnosis and genetic results. Confirmation of Barth Syndrome must be made prior to randomizing the subject. Subjects who complete all screening procedures during the Screening Period and continue to meet all trial requirements, including all inclusion and none of the exclusion criteria, will be randomized and enter Treatment Period 1.

Treatment Period 1: Treatment Period 1 will begin on the day of Treatment Period 1 Baseline (Pre-dose) Visit, which is defined as Treatment Period 1 Day 1. At the Treatment Period 1 Baseline Visit, following completion of all Baseline procedures described in the Trial Schedule, the subject will be administered IMP subcutaneously at the trial center. The Investigator (or designee) will also place a new AVIVO™ MPM System on the subject's chest and instruct the subject to continue to wear the System for approximately 7 consecutive days. At the discretion of the Investigator, the subject may return to the trial center on Treatment Period 1 Days 2 through 5 to receive a daily subcutaneous injection of IMP. At the Treatment Period 1 Baseline Visit, subjects (and caregivers) will be trained on the procedure for self-administration of IMP. The IMP should be administered at approximately the same time each day (e.g. early morning, noon, early afternoon, or evening). The Visiting Nurse will complete assessments at the Treatment Period 1 Week 1, 4, and 8 Nurse Visits as described in the Schedule of Visiting Nurse Assessments (Attachment 2). The trial center and Visiting Nurse will remind subjects to complete the age appropriate BTHS-SA daily throughout Treatment Period 1 and to apply and wear a new AVIVO™ MPM System daily for approximately 7 consecutive days immediately prior to the Treatment Period 1 Week 12 Visit. Treatment Period 1 will conclude with the Treatment Period 1 Week 12 visit at the trial center where the subjects will return all used vials, unused vials, and used AVIVO™ MPM Systems to the trial center.

Washout Period: The Washout will begin after the Treatment Period 1 Week 12 Visit and will last for 28 days (+7 days). During the Washout Period, subjects will continue to follow all trial requirements, including completing the age appropriate BTHS-SA daily.

Treatment Period 2: Treatment Period 2 will begin on the day of Treatment Period Pre-dose Visit, which is defined as Treatment Period 2 Day 1. At the Treatment Period 2 Pre-dose Visit, following completion of all Pre-dose procedures described in the Trial Schedule, the subject will be administered IMP subcutaneously at the trial center. The Investigator (or designee) will also place a new AVIVO™ MPM System on the subject's chest and instruct the subject to continue to wear the System for approximately 7 consecutive days. At the discretion of the Investigator, the subject may return to the trial center on Treatment Period 2 Days 2 through 5 to receive a daily subcutaneous injection of IMP. The IMP should be administered at approximately the same time each day (e.g. early morning, noon, early afternoon, or evening). The Visiting Nurse will complete assessments at the Treatment Period 2 Week 1, 4, and 8 Nurse Visits as described in the Schedule of Visiting Nurse Assessments (Attachment 2). The trial center and Visiting Nurse will remind subjects to complete the age appropriate BTHS-SA daily throughout Treatment Period 2 and to apply and wear a new AVIVO™ MPM System daily for approximately 7 consecutive days immediately prior to the Treatment Period 2 Week 12 Visit. Treatment Period 2 will conclude with the Treatment Period 2 Week 12 visit at the trial center where the subjects will return all used vials, unused vials, and used AVIVO™ MPM Systems to the trial center.

Part 1 Follow-Up Period: At the Treatment Period 2 Week 12 Visit, the subject and the Investigator will determine whether the subject will continue into Part 2 (confirming the subject meeting the Continuation Criteria). Subjects who will not continue into Part 2 will complete the Part 1 Follow-Up Period and Part 1 End-of-Trial Visit.

The Part 1 Follow-Up Period will begin after completion of Treatment Period 2 Week 12 and will last for 28 days (+7 days). During the Part 1 Follow-Up Period, subjects will continue to follow all trial requirements, including completing the age appropriate BTHS-SA daily. At the end of the Part 1 Follow-Up Period, subjects will return to the trial center for the Part 1 End-of-Trial/Early Discontinuation Visit for final safety and efficacy assessments as described in the Trial Schedule, and to return all trial materials/equipment.

For Part 1, an external Data and Safety Monitoring Board (DSMB) will be established to review safety data on a regular basis to ensure safety of all subjects enrolled.

6.1.2. Part 2

While there is no screening period for Part 2, subjects must meet the Part 2 Continuation Criteria. Subjects who decide not to continue to Part 2 at the Treatment Period 2 Week 12 Visit of Part 1 are not eligible to participate in Part 2. The Part 2 Schedule of Assessments is provided in Attachment 1. The Part 2 Trial Schematic is presented in Attachment 3.

Part 2 Treatment Period: The Part 2 Treatment Period will begin on the day after the Treatment Period 2 Week 12 Visit of Part 1. Subjects (or trained caregivers) will administer the IMP daily during the Part 2 Treatment Period. The subject will return to the clinical site for the Part 2 Week 12, 24, 36, 48, 72, 96, 120, 144, 168 Visits for assessments, to administer the IMP (subject or trained caregiver), and to return all used IMP supplies. Phone calls (or other forms of communication) will be made to the subject every 12 weeks between clinical site visits (i.e. weeks 60, 84, 108, 132, 156). During the Treatment Period, subjects will continue to follow all trial requirements.

Subjects who withdraw consent or are withdrawn from the trial by the investigator should be encouraged to complete an Early Discontinuation Visit as soon as possible and an effort should be made to complete and report the assessments as thoroughly as possible up to the date of withdrawal.

Part 2 Follow-Up Period: The Part 2 Follow-Up Period will begin after completion of the Part 2 Week 168 Visit and will last for 4 weeks. Subjects will continue to follow all trial requirements. Subjects will return to the clinical site for the Part 2 End-of-Trial Visit for final safety assessments, as described in the Part 2 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

6.2. Discussion of Design and Control

This is a randomized, double-blind, placebo-controlled, two-period crossover trial in subjects with genetically confirmed Barth Syndrome, followed by an open-label treatment extension.

Subjects will be randomized (1:1) to one of two sequence groups: 12-weeks of treatment with SC elamipretide in Treatment Period 1 followed by 12-weeks of treatment with placebo in Treatment Period 2 (separated by 4-week washout period), or vice versa.

A 4-week washout was selected to considerably reduce the likelihood of a carryover effect based on the known pharmacokinetics of elamipretide and anticipated turnover of mitochondria. The crossover design was selected because of the additional anticipated power due to subjects serving as their own control, given the anticipated scarcity of available subjects to participate in this study, due to the ultra-rare nature of this disease.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Part 2 is an open-label, uncontrolled treatment in which all subjects will receive elamipretide treatment for up to 168 weeks. This treatment period will allow for assessment of longer-term safety and tolerability in the target population, as well as allow for detection of less-frequent AEs.

The Part 1 and Part 2 Trial Schematics are presented in Attachment 3.

6.3. Trial Schedule

Trial procedures and their timing are summarized in the Part 1 and Part 2 Schedule of Assessments (trial center visits) (Attachment 1), Part 1 Schedule of Visiting Nurse Assessments (Attachment 2), and the Part 1 and Part 2 Trial Schematics (Attachment 3). A list of all clinical laboratory tests to be performed is found in Attachment 4. All study center visits should occur at approximately (±2 hours) the same time and after at least 3 hours of fasting. Days and Weeks are relative to the Pre-dose Visit of the respective Treatment Period in both Part 1 and Part 2.

6.3.1. Part 1

6.3.1.1. Screening Period: Day -28 to Day -1 (minimum of 7 days)

- Complete the age appropriate BTHS-SA (as described in Section 6.4.12) daily during the Screening Period

6.3.1.1.1. *Screening Visit*

NOTE: The 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should be completed in the order described below and on the same day.

- Review and sign the Informed Consent Form (ICF)
- Record demographics (age, gender, ethnicity, race)
- Review all inclusion and exclusion criteria
- Record relevant medical history (as described in Section 6.4.1)
- Record concomitant medication (including supplements and vitamins) (as described in Section 6.4.1)
- Complete a physical examination (as described in Section 6.4.2)
- Collect vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)

- Draw blood and urine for clinical laboratory testing and urinalysis as outlined in Attachment 4 (as described in Section 6.4.5)
- Collect blood and urine for biomarker testing, as outlined in Attachment 4 (as described in Section 6.4.6)
- Collect blood spot (as described in Section 6.4.7)
- Complete the 2-D and 3-D echocardiograms (as described in Section 6.4.8)
- Complete the Columbia Suicide Severity Rating Scale (C-SSRS) "Lifetime Recent" (as described in Section 6.4.10 and outlined in Attachment 5)
- Complete the age appropriate PROMIS Short Form Fatigue assessment (as described in Section 6.4.11)
- Complete the age appropriate Patient Global Impression (PGI) Scales (as described in Section 6.4.13)
- Complete the Clinician Global Impression (CGI) Scales (as described in Section 6.4.14)
- Complete the age appropriate Caregiver Global Impression (CaGI) Scales (as described in Section 6.4.15)
- Complete the age appropriate EQ-5D instrument (as described in Section 6.4.16)
- Conduct the 6MWT (as described in Section 6.4.17 and as outlined in Attachment 14)
- Complete the 5XSST which should be started after completion of 6MWT and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.18 and as outlined in Attachment 15)
- Complete the HHD testing which should be started after completion of 5XSST and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.19)
- Complete the SWAY Application Balance Assessments (as described in Section 6.4.20 and outlined in Attachment 13) which should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes)
- Train subject on application of the AVIVO™ MPM System. Apply AVIVO™ MPM System to the subject's chest. The AVIVO™ MPM System should be used for approximately 7 consecutive days following the visit (as described in Section 6.4.9)
- Schedule next center visit

6.3.1.2. Treatment Period 1

- Complete the age appropriate BTHS-SA (as described in Section 6.4.11) daily during Treatment Period 1
- Subjects (or trained caregivers) will administer IMP on a daily basis at approximately the same time each day (e.g. early morning, noon, early afternoon, or evening)

- Subjects will be instructed and reminded at approximately Week 11, to apply and wear a new AVIVO™ MPM System for approximately 7 consecutive days immediately prior to the Treatment Period 1 Week 12 Visit

6.3.1.2.1. *Treatment Period 1 Baseline (Pre-dose) Visit (Day 1)*

NOTE: Subjects who have been deemed eligible during Screening Period will return for randomization and the following procedures will be performed. All trial procedures must be completed prior to administering IMP. The decision to have a subject return for the Days 2 through 5 Visits and on the schedule of Visiting Nursing Visits for both Treatment Period 1 and Treatment Period 2 should be made and documented prior to the Treatment Period 1 Baseline Visit. The 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should be completed in the order described below and on the same day.

- Review all inclusion and exclusion criteria
- Document AEs related to a trial procedure and/or meet seriousness criteria that occurred since the signing of the informed consent form as described in Section 9.11
- Update relevant medical history during the Screening Period (as described in Section 6.4.1)
- Update concomitant medication/procedures (including supplements and vitamins) during the Screening Period (as described in Section 6.4.1)
- Randomize subject
- Complete a physical examination (as described in Section 6.4.2)
- Collect vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood and urine for clinical laboratory testing and urinalysis as outlined in Attachment 4 (as described in Section 6.4.5)
- Collect blood and urine for biomarker testing, and metabolomics as outlined in Attachment 4 (as described in Section 6.4.6) (urine metabolomics should be first morning void urine sample)
- Collect blood spot (as described in Section 6.4.7)
- Complete the 2-D and 3-D echocardiograms (as described in Section 6.4.8)
- Complete the C-SSRS “Since Last Visit” (as described in Section 6.4.10 and outlined in Attachment 6)
- Complete the age appropriate PROMIS Short Form Fatigue assessment (as described in Section 6.4.11)
- Complete the age appropriate PGI Scales (as described in Section 6.4.13)
- Complete the CGI Scales (as described in Section 6.4.14)

- Complete the age appropriate CaGI Scales (as described in Section 6.4.15)
- Complete the age appropriate EQ-5D instrument (as described in Section 6.4.16)
- Conduct the 6MWT (as described in Section 6.4.17 and as outlined in Attachment 14)
- Complete the 5XSST which should be started after completion of 6MWT and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.18 and as outlined in Attachment 15)
- Complete the HHD testing which should be started after completion of 5XSST and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.19)
- Complete the SWAY Application Balance Assessments (as described in Section 6.4.20 and outlined in Attachment 13) which should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes)
- Inject the IMP
- Apply a new AVIVO™ MPM System to the subject's chest. The new AVIVO™ MPM System should be used for approximately 7 consecutive days following the visit (as described in Section 6.4.9)
- Schedule next center visit and discuss visit schedule and how to schedule the Visiting Nurse service

6.3.1.2.2. *Treatment Period 1 Days 2 through 5 Visits (optional)*

- Document AEs
- Inject the IMP

6.3.1.2.3. *Treatment Period 1 Visiting Nurse Visits: Week 1 (Day 8 ± 1), Week 4 (Day 29 ± 2), and Week 8 (Day 57 ± 2)*

A Visiting Nurse will visit the subject at the Treatment Period 1 Week 1 (Day 8 ± 1), Week 4 (Day 29 ± 2), and Week 8 (Day 57 ± 2). The Visiting Nurse will compete assessments as described in the Schedule of Visiting Nurse Assessments (Attachment 2).

6.3.1.2.4. *Treatment Period 1 Week 12 Visit (Day 85 ±7)*

NOTE: Subjects will be instructed and reminded at approximately Week 11, to apply and wear a new AVIVO™ MPM System for approximately 7 consecutive days immediately prior to the Treatment Period 1 Week 12 Visit. Subjects should be instructed to administer the IMP on the day of Treatment Period 1 Week 12 Visit, prior to returning to the trial center. The 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should be completed in the order described below and on the same day.

- Update concomitant medication/procedures (including supplements and vitamins) during the Screening Period (as described in Section 6.4.1)
- Document AEs

- Complete a physical examination (as described in Section 6.4.2)
- Collect vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood and urine for clinical laboratory testing and urinalysis as outlined in Attachment 4 (as described in Section 6.4.5)
- Collect blood and urine for biomarker testing, and metabolomics as outlined in Attachment 4 (as described in Section 6.4.6) (urine metabolomics should be first morning void urine sample)
- Collect blood spot (as described in Section 6.4.7)
- Complete the 2-D and 3-D echocardiograms (as described in Section 6.4.8)
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.4.10 and outlined in Attachment 6)
- Complete the age appropriate PROMIS Short Form Fatigue assessment (as described in Section 6.4.11)
- Complete the age and Treatment Period appropriate PGI Scales (as described in Section 6.4.13)
- Complete the Treatment Period appropriate CGI Scales (as described in Section 6.4.14)
- Complete the age and Treatment Period appropriate CaGI Scales (as described in Section 6.4.15)
- Complete the age appropriate EQ-5D instrument (as described in Section 6.4.16)
- Conduct the 6MWT (as described in Section 6.4.17 and as outlined in Attachment 14)
- Complete the 5XSST which should be started after completion of 6MWT and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.18 and as outlined in Attachment 15)
- Complete the HHD testing which should be started after completion of 5XSST and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.19)
- Complete the SWAY Application Balance Assessments (as described in Section 6.4.20 and outlined in Attachment 13) which should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes)
- Collect all used and unused IMP vials from the subject
- Schedule next center visit

6.3.1.3. Washout Period (28 days +7)

Washout will be 28 days (+7 days) in duration. If all used and unused vials were not returned at the Treatment Period 1 Week 12 Visit, an unscheduled Visiting Nurse Visit may be scheduled

to collect all remaining vials. The age appropriate BTHS-SA (as described in Section 6.4.12) should be completed daily during the Washout Period.

6.3.1.4. Treatment Period 2

- Complete the age appropriate BTHS-SA (as described in Section 6.4.11) daily during Treatment Period 2
- Subjects (or trained caregivers) will administer IMP on a daily basis at approximately the same time each day (e.g. early morning, noon, early afternoon, or evening)
- Subjects will be instructed and reminded at approximately Week 11, to apply and wear a new AVIVO™ MPM System for approximately 7 consecutive days immediately prior to the Treatment Period 2 Week 12 Visit

6.3.1.4.1. *Treatment Period 2 Pre-dose Visit (Day 1)*

NOTE: All trial procedures must be completed prior to administering IMP. The 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should be completed in the order described below and on the same day.

- Document AEs
- Update concomitant medication/procedures (including supplements and vitamins) (as described in Section 6.4.1)
- Complete a physical examination (as described in Section 6.4.2)
- Collect vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood and urine for clinical laboratory testing and urinalysis as outlined in Attachment 4 (as described in Section 6.4.5)
- Collect blood and urine for biomarker testing, and metabolomics as outlined in Attachment 4 (as described in Section 6.4.6) (urine metabolomics should be first morning void urine sample)
- Collect blood spot (as described in Section 6.4.7)
- Complete the 2-D and 3-D echocardiograms (as described in Section 6.4.8)
- Complete the C-SSRS “Since Last Visit” (as described in Section 6.4.10 and outlined in Attachment 6)
- Complete the age appropriate PROMIS Short Form Fatigue assessment (as described in Section 6.4.11)
- Complete the age appropriate PGI Scales (as described in Section 6.4.13)
- Complete the CGI Scales (as described in Section 6.4.14)
- Complete the age appropriate CaGI Scales (as described in Section 6.4.15)

- Complete the age appropriate EQ-5D instrument (as described in Section 6.4.16)
- Conduct the 6MWT (as described in Section 6.4.17 and as outlined in Attachment 14)
- Complete the 5XSST which should be started after completion of 6MWT and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.18 and as outlined in Attachment 15)
- Complete the HHD testing which should be started after completion of 5XSST and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.19)
- Complete the SWAY Application Balance Assessments (as described in Section 6.4.20 and outlined in Attachment 13) which should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes)
- Inject IMP
- Apply a new AVIVO™ MPM System to the subject's chest. The new AVIVO™ MPM System should be used for approximately 7 consecutive days following the visit (as described in Section 6.4.9)
- Schedule next center visit and discuss home (or other Investigator agreed upon location) visit schedule by the Visiting Nurse

6.3.1.4.2. *Treatment Period 2 Days 2 through 5 Visits (optional)*

- Document AEs
- Inject IMP

6.3.1.4.3. *Treatment Period 2 Visiting Nurse Visits: Week 1 (Day 8 ± 1), Week 4 (Day 29 ± 2), and Week 8 (Day 57 ± 2)*

A Visiting Nurse will visit the subject at the Treatment Period 2 Week 1 (Day 8 ± 1), Week 4 (Day 29 ± 2), and Week 8 (Day 57 ± 2). The Visiting Nurse will compete assessments as described in the Schedule of Visiting Nurse Assessments (Attachment 2).

6.3.1.4.4. *Treatment Period 2 Week 12 Visit (Day 85 ± 7)*

NOTE: Subjects will be instructed and reminded at approximately Week 11, to apply and wear a new AVIVO™ MPM System for approximately 7 consecutive days immediately prior to the Treatment Period 2 Week 12 Visit. Subjects should be instructed to administer the IMP on the day of Treatment Period 2 Week 12 Visit, prior to returning to the trial center. The 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should be completed in the order described below and on the same day.

- Update concomitant medication/procedures (including supplements and vitamins) during the Screening Period (as described in Section 6.4.1)
- Document AEs
- Complete a physical examination (as described in Section 6.4.2)

- Collect vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood and urine for clinical laboratory testing and urinalysis as outlined in Attachment 4 (as described in Section 6.4.5)
- Collect blood and urine for biomarker testing, and metabolomics as outlined in Attachment 4 (as described in Section 6.4.6) (urine metabolomics should be first morning void urine sample)
- Collect blood spot (as described in Section 6.4.7)
- Complete the 2-D and 3-D echocardiograms (as described in Section 6.4.8)
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.4.10 and outlined in Attachment 6)
- Complete the age appropriate PROMIS Short Form Fatigue assessment (as described in Section 6.4.11)
- Complete the age and Treatment Period appropriate PGI Scales (as described in Section 6.4.13)
- Complete the Treatment Period appropriate CGI Scales (as described in Section 6.4.14)
- Complete the age and Treatment Period appropriate CaGI Scales (as described in Section 6.4.15)
- Complete the age appropriate EQ-5D instrument (as described in Section 6.4.16)
- Conduct the 6MWT (as described in Section 6.4.17 and as outlined in Attachment 14)
- Complete the 5XSST which should be started after completion of 6MWT and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.18 and as outlined in Attachment 15)
- Complete the HHD testing which should be started after completion of 5XSST and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.19)
- Complete the SWAY Application Balance Assessments (as described in Section 6.4.20 and outlined in Attachment 13) which should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes)
- Collect all used and unused IMP vials from the subject
- Schedule next center visit
    - Post-treatment Part 1 Follow-Up Visit for subjects not continuing into Part 2.
    - Week 28 visit for subjects continuing into Part 2.

6.3.1.5. Part 1 Follow-Up Period (28 days +7) (for subjects not continuing into Part 2)

At Treatment Period 2 Week 12 Visit, the subject and the Investigator will determine whether the subject will continue into Part 2 (confirming the subject meeting the Continuation Criteria). Subjects who will not continue into Part 2 will complete the Part 1 Follow-Up Period and Part 1 End-of-Trial Visit.

For subjects not continuing into Part 2, the Part 1 Follow-Up Period will begin after completion of the Treatment Period 2 Week 12 Visit.

The Part 1 Follow-Up Period will be 4 weeks in duration. If all used and unused vials were not returned at the Treatment Period 2 Week 12 Visit, an unscheduled Visiting Nurse Visit may be scheduled to collect all remaining vials. The age appropriate BTHS-SA (as described in Section 6.4.12) should be completed daily during the Part 1 Follow-up Period. Subjects will return to the clinical site for the Part 1 End-of-Trial Visit for final safety assessments, as described in the Part 1 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

6.3.1.5.1. *End-of-Trial/Early Discontinuation Visit (Day 113 + 7 days) /Early Discontinuation (for subjects not continuing into Part 2)*

NOTE: The 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should be completed in the order described below and on the same day.

- Update concomitant medication/procedures (including supplements and vitamins) since the last visit (as described in Section 6.4.1)
- Document AEs
- Complete a physical examination (as described in Section 6.4.2)
- Collect vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood and urine for clinical laboratory testing and urinalysis as outlined in Attachment 4 (as described in Section 6.4.5)
- Collect blood and urine for biomarker testing, and metabolomics as outlined in Attachment 4 (as described in Section 6.4.6) (urine metabolomics should be first morning void urine sample)
- Collect blood spot (as described in Section 6.4.7)
- Complete the 2-D and 3-D echocardiograms (as described in Section 6.4.8)
- Complete the C-SSRS “Since Last Visit” (as described in Section 6.4.10 and outlined in Attachment 6)
- Complete the age appropriate PROMIS Short Form Fatigue assessment (as described in Section 6.4.11)
- Complete the age appropriate PGI Scales (as described in Section 6.4.13)

- Complete the CGI Scales (as described in Section 6.4.14)
- Complete the age appropriate CaGI Scales (as described in Section 6.4.15)
- Complete the age appropriate EQ-5D instrument (as described in Section 6.4.16)
- Conduct the 6MWT (as described in Section 6.4.17 and as outlined in Attachment 14)
- Complete the 5XSST which should be started after completion of 6MWT and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.18 and as outlined in Attachment 15)
- Complete the HHD testing which should be started after completion of 5XSST and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.19)
- Complete the SWAY Application Balance Assessments (as described in Section 6.4.20 and outlined in Attachment 13) which should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes)
- Collect all used and unused vials from the subject

6.3.2. Part 2

6.3.2.1. Part 2 Treatment Period

The Part 2 Treatment Period will include both clinical site visits and phone calls (or other forms of communication) from the site staff.

6.3.2.1.1. *Clinical Site Visits: Weeks 12 (± 1 week), and Weeks 24, 36, 48, 72, 96, 120, 144, and 168 (± 2 weeks for each visit)*

At all clinical site visits during the Part 2 Treatment Period visits, subjects will return used IMP supplies. At the Part 2 Week 168 visit, subjects will return all trial-related supplies. On the day of the Visit that the PK samples are collected (at the earliest clinical site visit in Part 2 [at or after the Week 12 Visit in Part 2]), subjects should be instructed to administer the IMP at the trial center..

NOTE: The 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should be completed in the order described below and on the same day.

- Update concomitant medication/procedures (including supplements and vitamins) since the last visit (as described in Section 6.4.1)
- Document AEs
- Complete a physical examination (as described in Section 6.4.2)
- Collect vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood and urine for clinical laboratory testing and urinalysis as outlined in Attachment 4 (as described in Section 6.4.5)

- Collect blood and urine for biomarker testing, and metabolomics as outlined in Attachment 4 (as described in Section 6.4.6) (urine metabolomics should be first morning void urine sample)
- Collect blood spot (as described in Section 6.4.7)
- Complete the 2-D and 3-D echocardiograms (as described in Section 6.4.8)
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.4.10 and outlined in Attachment 6)
- Complete the age appropriate BTHS-SA (as described in Section 6.4.12)
- Complete the age appropriate PROMIS Short Form Fatigue assessment (as described in Section 6.4.11)
- Complete the age appropriate PGI Scales (as described in Section 6.4.13)
- Complete the CGI Scales (as described in Section 6.4.14)
- Complete the age appropriate CaGI Scales (as described in Section 6.4.15)
- Complete the age appropriate EQ-5D instrument (as described in Section 6.4.16)
- Conduct the 6MWT (as described in Section 6.4.17 and as outlined in Attachment 14)
- Complete the 5XSST which should be started after completion of 6MWT and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.18 and as outlined in Attachment 15)
- Complete the HHD testing which should be started after completion of 5XSST and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.19)
- Complete the SWAY Application Balance Assessments (as described in Section 6.4.20 and outlined in Attachment 13) which should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes)
- Collect all used and unused vials from the subject
- Draw blood for PK testing as described in Section 6.4.21 (at the earliest clinical site visit in Part 2 (at or after the Week 12 Visit in Part 2):
    - Pre-dose (-30 min)
    - 0.5h (± 5 min)
    - 1h (± 10 min)
    - 2h (± 15 min)
    - 4h (± 15 min)

6.3.2.1.2. *Phone Calls (or other forms of communication): Part 2 Weeks 60, 84, 108, 132, 156 (± 2 weeks for each visit)*

A phone call (or other forms of communication) from the site will be made to the subject to assess AEs/ADEs and concomitant medications (see Attachment 17 for a sample of the telephone script to use).

6.3.2.2. Part 2 Follow-Up Period (4 weeks [+7 days])

The Part 2 Follow-Up Period will begin after completion of the Part 2 Week 168 Visit and will last for 4 weeks. Subjects will continue to follow all trial requirements. Subjects will return to the clinical site for the Part 2 End-of-Trial Visit for final assessments, as described in the Part 2 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

6.3.2.2.1. *Part 2 End-of-Trial/Early Discontinuation Visit (Week 172 +7 days)*

NOTE: The 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should be completed in the order described below and on the same day.

- Update concomitant medication/procedures (including supplements and vitamins) since the last visit (as described in Section 6.4.1)
- Document AEs
- Complete a physical examination (as described in Section 6.4.2)
- Collect vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood and urine for clinical laboratory testing and urinalysis as outlined in Attachment 4 (as described in Section 6.4.5)
- Collect blood and urine for biomarker testing, and metabolomics as outlined in Attachment 4 (as described in Section 6.4.6) (urine metabolomics should be first morning void urine sample)
- Collect blood spot (as described in Section 6.4.7)
- Complete the 2-D and 3-D echocardiograms (as described in Section 6.4.8)
- Complete the C-SSRS “Since Last Visit” (as described in Section 6.4.10 and outlined in Attachment 6)
- Complete the age appropriate BTHS-SA (as described in Section 6.4.12)
- Complete the age appropriate PROMIS Short Form Fatigue assessment (as described in Section 6.4.11)
- Complete the age appropriate PGI Scales (as described in Section 6.4.13)
- Complete the CGI Scales (as described in Section 6.4.14)
- Complete the age appropriate CaGI Scales (as described in Section 6.4.15)

- Complete the age appropriate EQ-5D instrument (as described in Section 6.4.16)
- Conduct the 6MWT (as described in Section 6.4.17 and as outlined in Attachment 14)
- Complete the 5XSST which should be started after completion of 6MWT and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.18 and as outlined in Attachment 15)
- Complete the HHD testing which should be started after completion of 5XSST and after at least 5 minutes rest (should not be more than 30 minutes) (as described in Section 6.4.19)
- Complete the SWAY Application Balance Assessments (as described in Section 6.4.20 and outlined in Attachment 13) which should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes)
- Collect all used and unused vials from the subject

6.4. Trial Assessments

The following section describes trial assessments occurring during the trial. Trial assessments and their timing are summarized in the Part 1 and Part 2 Schedule of Assessments (trial center visits) (Attachment 1) and the Schedule of Visiting Nurse Assessments (Attachment 2).

6.4.1. Medical History and Concomitant Medications/Procedures

Relevant medical history (in the opinion of the Investigator) and any concomitant medications will be recorded during the Screening Visit. At the Baseline Visit, a review of any additional medical history and/or new concomitant medication/procedures that occurred during the Screening Period will be taken. Concomitant medications/procedures should be updated and recorded at each center visit.

6.4.2. Physical Examination

During all trial center visits, a complete physical examination will be performed at each center visit. The physical examination will include a full review of the following systems: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system, and weight. Height will be measured during all physical examinations.

6.4.3. Vital signs

During all trial center visits and Visiting Nurse Visits, the vital signs measurements will include temperature, heart rate, respiration rate and blood pressure, recorded in the sitting position after at least 5 minutes rest.

6.4.4. Electrocardiograms (ECGs)

A 12-lead ECG will be obtained after the subjects has rested quietly for 10 minutes in the supine position. ECG intervals (PR, RR, QRS, QT), heart rate and ECG findings will be

recorded for each subject. Based on signs or symptoms, additional 12-lead ECGs may be performed.

6.4.5. Clinical Laboratory Testing

Sample collection, processing and handling details are provided in the Laboratory Manual.

6.4.5.1. Blood Chemistries

Blood will be collected at trial center visits and Visiting Nurse Visits. Analysis will include testing for parameters included in Attachment 4.

6.4.5.2. Hematology

Blood will be collected at trial center visits and Visiting Nurse Visits. Analysis will include testing for parameters included in Attachment 4.

6.4.5.3. Urinalysis

Urine will be collected at trial center visits and Visiting Nurse Visits. Analysis will include testing for parameters included in Attachment 4.

6.4.6. Biomarker Testing

Sample collection, processing and handling details are provided in the Laboratory Manual. Blood and urine will be collected for analysis of biomarkers as outlined in Attachment 4. Urine metabolomics should be first morning void urine sample. Additional blood samples will be collected and stored, for assessing the immunogenicity potential of the IMP, at the Baseline Visit of Treatment Period 1, Treatment Period 2 Week 12 Visit, and (if applicable) Part 1 or Part 2 Early Discontinuation Visits.

6.4.7. Blood Spot

A blood spot test will be completed at trial center visits. Analysis will include testing for parameters included in Attachment 4.

6.4.8. 2-D and 3-D Echocardiographs

2-D and 3-D echocardiograms will be performed. Parameters to be assessed include:

2-D

- Left ventricular (LV) end-diastolic volume (mL)
- LV end-systolic volumes (mL)
- LV ejection fraction (EF) (%)
- LV dimensions
    - LVSd (cm)
    - LVSs (cm)

    - LVIDd (cm)
    - LVIDs (cm)
    - LVPWd (cm)
    - LVPWs (cm)
- LV fractional shortening (%)
- LV global longitudinal strain (triplane) (%)
- LV peak systolic strain
    - apical 4 chamber view (%)
    - apical 2 chamber view (%)
    - apical LAX view (%)
- Left atrial volume (mL)
- LV mass (g)
- Diastology
    - Peak E (m/s)
    - Peak A (m/s)
    - Medial MV annulus e (m/s)
    - Medial MV annulus a (m/s)
    - Lateral MV annulus e (m/s)
    - Lateral MV annulus a (m/s)
- Measurement of non-compaction (Chin and Jenni methods):
    - Chin: ratio (X/Y) at LV apex at end-diastole
    - Jenni: ratio (NC/C) at LV apex at end-systole
- Aortic valve regurgitation (semi-quantitative) (trivial, mild, moderate, severe)
- Mitral regurgitation (semi-quantitative) (trivial, mild, moderate, severe)
- Tricuspid regurgitation (semi-quantitative) (trivial, mild, moderate, severe)
- Structural abnormalities

<u>3-D</u>

- LV end-diastolic volume (mL)
- LV end-systolic volumes (mL)
- LV EF%

6.4.9. AVIVO™ Mobile Patient Management (MPM) System

The AVIVO™ Mobile Patient Management (MPM) System is intended to continuously measure, record and periodically transmit physiological data including, but not limited to, ECG and activity (accelerometry).

In Part 1, starting at the Screening Visit, subjects will be provided with an AVIVO™ MPM System which will be applied, as instructed in the product manual, at trial center visits by the Investigator (or designee) or subject (or trained caregiver). The Investigator (or designee) will educate the subject on appropriate application and use of the AVIVO™ MPM System. A new AVIVO™ MPM System will also be provided and applied at the trial center at Treatment Period 1 Baseline and Treatment Period 2 Pre-dose Visits. Subjects will be instructed and reminded to apply and wear a new AVIVO™ MPM System at approximately Week 11, immediately prior to the Treatment Period 1 Week 12 Visit and the Treatment Period 2 Week 12 Visit. Subjects will be instructed to wear each AVIVO™ MPM System for approximately 7 consecutive days after each application. Subjects will return all AVIVO™ MPM Systems by the completion of his/her participation in the trial.

The AVIVO™ MPM System will not be used in Part 2.

6.4.10. Columbia Suicide Severity Rating Scale (C-SSRS)

At the Screening Visit, the C-SSRS "Lifetime Recent" will be completed and recorded. The C-SSRS "Lifetime Recent" is included in Attachment 5. At all other trial center visits, the C-SSRS "Since Last Visit" will be recorded. The C-SSRS "Since Last Visit" is included in Attachment 6.

6.4.11. PROMIS Short Form Fatigue

The age appropriate PROMIS Short Form Fatigue should be completed. The age appropriate PROMIS Short Form Fatigue instruments are provided in Attachment 7. For subjects ≥ 18 years of age at the Screening Visit, the PROMIS Adult Short Form Fatigue should be completed. Subjects 12-17 years of age at the Screening Visit, the PROMIS Pediatric Short Form Fatigue should be completed for the duration of the trial.

6.4.12. BarTH Syndrome Symptom Assessment (BTHS-SA)

In Part 1, the age appropriate BTHS-SA should be completed daily by the subject in a diary starting at the Screening Visit and continued until the Part 1 Treatment Period 2 Week 12 Visit (for subjects continuing into Part 2) or Part 1 End-of-Trial/Early Discontinuation Visit (for subjects not continuing into Part 2). In Part 2, the age appropriate BTHS-SA should be completed ONLY at the clinical site visits. The age appropriate BTHS-SAs are provided in Attachment 8. For subjects ≥ 16 years of age at the Screening Visit, the BTHS-SA Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the BTHS-SA Adolescent should be completed for the duration of the trial.

6.4.13. Patient Global Impression (PGI) Scales

The age appropriate PGI Scales should be completed to assess their overall assessment of their symptoms related to their diagnosis of Barth Syndrome. The age appropriate PGI Scales are

provided in Attachment 9. For subjects ≥ 16 years of age at the Screening Visit, the PGI Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the PGI Adolescent should be completed for the duration of the trial. The age and Treatment Period appropriate PGI of Change Scales should be completed only at Week 12 of Treatment Period 1 and Week 12 of Treatment Period 2.

6.4.14. Clinician Global Impression (CGI) Scales

The Investigator or designee will provide an overall assessment of the subject's symptoms related to their diagnosis of Barth Syndrome at all trial center visits. The CGI Scales are provided in Attachment 10. The same Investigator or designee should administer the CGI at each visit for a particular subject. The Treatment Period appropriate CGI of Change Scale should be completed only at Week 12 of Treatment Period 1 and Week 12 of Treatment Period 2.

6.4.15. Caregiver Global Impression (CaGI) Scales

The age appropriate CaGI Scales should be completed (if applicable) by a caregiver of the subject to assess the caregiver's overall assessment of the subject's symptoms related to their diagnosis of Barth Syndrome. The age appropriate CaGI Scales are provided in Attachment 11. The same caregiver should complete the age appropriate CaGI at each visit for a particular subject. For subjects ≥ 16 years of age at the Screening Visit, the CaGI Adult should be completed by the caregiver. Subjects 12-15 years of age at the Screening Visit, the CaGI Adolescent should be completed by the caregiver for the duration of the trial. The age and Treatment Period appropriate CaGI of Change Scales should be completed only at Week 12 of Treatment Period 1 and Week 12 of Treatment Period 2.

6.4.16. EQ-5D

An age appropriate EQ-5D should be completed. The age appropriate EQ-5D instrument is provided in Attachment 12. For subjects ≥ 16 years of age at the Screening Visit, the EQ-5D-5L should be completed. Subjects 12-15 years of age at the Screening Visit, the EQ-5D-Y should be completed for the duration of the trial.

6.4.17. 6-Minute Walk Test (6MWT)

At all trial center visits, the distance walked (in meters) during the 6MWT will be recorded. The 6MWT instructions are provided in Attachment 14. The Investigator (or designee) conducting the 6MWT should not be the same Investigator (or designee) completing the safety assessments for a particular subject.

6.4.18. 5X Sit to Stand Test (5XSST)

At all trial center visits, the time (in seconds) to complete the 5XSST will be recorded. The 5XSST instructions are provided in Attachment 15. The 5XSST Test should be performed after completion of the 6MWT and at least 5 minutes rest (should not be more than 30 minutes). The Investigator (or designee) conducting the 5XSST should not be the same Investigator (or designee) completing the safety assessments for a particular subject.

6.4.19. Handheld Dynamometry (HHD)

The day of assessment the handheld dynamometer will be calibrated using a 2-kg weight:

1. Using a 2-kg weight:
2. Turn the handheld dynamometer on with the round flat transducer head up and the reading frame facing tester. Place in foam carrying case.
3. Press reset button.
4. Place calibration weight on the transducer pad. Verify the weight is centered and stable.
5. Read force reading displayed in "read force" LCD while weight is resting on the transducer pad.

If there is more than a 5% difference, contact manufacturer and do not conduct the HHD testing with that dynamometer. At all trial center visits, HHD assessments will be completed and recorded. The HHD assessments should be performed after completion of the 5XSST and at least 5 minutes rest (should not be more than 30 minutes). Handheld dynamometry will assess the knee extensors of both legs. Subjects should be positioned in a short sitting position on adjustable height treatment mat with hips and knee flexed to 90 degrees with feet unsupported. The handheld dynamometer should be positioned on the anterior surface of lower leg, just proximal to the ankle. The tester position should be kneeling in front of the subject. Subject will be provided with the following instructions: "Straighten your knee, push, push, push." Strength will be assessed via "make technique" where tester will resist/match the maximum isometric contraction for 5 seconds to allow full muscle fiber recruitment. Perform on right lower extremity and then left and repeat (right, left, right, left). The average of the two attempts for each extremity will be analyzed.

The Investigator (or designee) conducting the HHD should not be the same Investigator (or designee) completing the safety assessments for a particular subject.

6.4.20. SWAY Application Balance Assessments

The SWAY Application Balance Assessments will be complete and recorded. The SWAY Application Balance Assessments instructions are provided in Attachment 13. The Investigator (or designee) conducting the SWAY Application Balance Assessments should not be the same Investigator (or designee) completing the safety assessments for a particular subject. The SWAY Application Balance Assessments should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes).

6.4.21. Pharmacokinetic (PK) Sampling

To characterize the PK of elamipretide and metabolites, PK sampling will be conducted at defined time points at the earliest clinical site visit in Part 2 (at or after the Week 12 Visit in Part 2). To reduce trial procedure burden, PK sampling may be completed during the earliest scheduled clinical site visit in Part 2 (at or after the Week 12 Visit in Part 2) or at an independent clinical site visit. Additionally, to reduce the need for multiple venipunctures, in the opinion of the Investigator, a venous catheter may be used for PK sample collection. Blood

samples for PK determinations of elamipretide and metabolites concentrations will be collected as follows:

- Pre-dose (-30 min)
- 0.5h (± 5 min)
- 1h (± 10 min)
- 2h (± 15 min)
- 4h (± 15 min)

Sample collection, processing and handling details are provided in the Laboratory Manual.

6.5. Data and Safety Monitoring Board

For Part 1, an external DSMB meeting is to be held at regular intervals to evaluate the safety of this study. The role of the DSMB members is to evaluate the safety within each treatment group on an ongoing basis in order to determine whether any undue safety concerns are observed, and thus whether the study should be allowed to continue enrollment.

A detailed DSMB charter will be prepared by the Sponsor and agreed to by all DSMB members before initiation of enrollment in this study. This charter will document the timing, membership, analysis content, and review procedures for each DSMB meeting. Safety analyses will include, at a minimum, summaries of study disposition and all TEAEs, SAEs, deaths, and discontinuations due to AEs, laboratory results, and individual subject listings of selected safety data.

7. TRIAL POPULATION

The inclusion and exclusion criteria for participation in this trial are provided below. All screening assessments must be completed during the Screening Period, but may be performed on different days. Screening assessments should not be repeated, and subjects cannot be re-screened without the Sponsor's approval. If a subject is re-screened, they will maintain their original screening number. Subjects may only be enrolled into the trial one time.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

7.1. Inclusion Criteria

A subject must meet ALL of the following Inclusion Criteria at the Baseline Visit:

1. Willing and able to provide signed informed consent form (ICF) prior to participation in any trial-related procedures. If applicable, informed consent in writing from parent(s) or legally-acceptable representative(s) and, informed assent from subject (if age appropriate according to local requirements) should be provide
2. Agrees to adhere to the trial requirements for the length of the trial
3. Genetically confirmed Barth Syndrome in the opinion of the Investigator
4. Male aged ≥ 12 years
5. At the Screening Visit, subject body weight and estimated glomerular filtration rate (eGFR) meeting one of the following:
    a. Body weight >30 kg AND eGFR ≥ 90 mL/min/1.73 m^2 at the Screening visit
    b. Body weight >40 kg AND eGFR ≥ 60 mL/min/1.73 m^2 at the Screening visit

    eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation:

    eGFR (mL/min/1.73 m^2) = 175 x (SCr*)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African American) *=serum creatinine
6. Ambulatory and impaired, in the opinion of the Investigator, during the 6-Minute Walk Test at the Baseline Visit
7. Subject has been on stable (unchanged and constant) medications (including over-the-counter treatments, vitamins, or supplements), or medications that will not impact the safety or efficacy endpoints of the trial, in the opinion of the Investigator for at least 30 days prior to the Baseline Visit
8. Male subjects with female partners of child-bearing potential must be willing to use a highly effective method of contraception (see Section 9.11.1 for details) from the Screening Visit through at least 2 months following the last injection

7.2. Exclusion Criteria

A subject must NOT meet any of the following exclusion criteria at the Baseline Visit:

1. Participated in another interventional clinical trial within 30 days of or is currently enrolled in a non-interventional clinical trial at the Baseline Visit judged by the Investigator to be potentially confounding with the current trial
2. Any prior or current medical condition that, in the judgment of the Investigator, would prevent the subject from safely participating in and/or completing all trial requirements
3. Undergone an in-patient hospitalization within 30 days prior to the Baseline Visit or is likely to need in-patient hospitalization or surgical procedure during the course of the trial
4. Subject is undergoing an apparent pubertal growth spurt in the opinion of the Investigator
5. Subject has uncontrolled hypertension in the judgment of the Investigator (e.g. consistently elevated above >160 mmHg systolic or >100 mmHg diastolic despite appropriate treatment)
6. Subject has a history of clinically significant hypersensitivity or allergy to any of the excipients contained in the investigational medicinal product (IMP)
7. Subject has a history of active substance abuse during the year before the Baseline Visit, or is thought, for any reason, likely not to be compliant in the opinion of the Investigator
8. History of heart transplantation or current placement (or within the past year) on the waiting list for a heart transplantation
9. a. For subjects with an implantable cardioverter defibrillator (ICD): the known occurrence of ICD therapy/discharge in the 3 months prior to the Baseline Visit and/or expected to undergo re-implantation during the conduct of the study
   b. For subjects without an implantable cardioverter defibrillator (ICD): expected to undergo an implantation of an ICD during the conduct of the study
10. Currently receiving treatment with chemotherapeutic agents or immunosuppressant agents or has received prior radiation therapy to the chest
11. Recipient of stem cell or gene therapy or is currently being treated by a therapeutic investigational device

7.3. Part 2 Continuation Criteria

A subject must meet all of the following Part 2 Continuation Criteria at the Treatment Period 2 Week 12 Visit of Part 1 to be eligible for Part 2:

1. Subjects must continue to be able and willing to adhere to the trial requirements
2. Subject is appropriate to continue in Part 2 (i.e. subject was compliant in Part 1), in the opinion of the Investigator

3. Subject has not had a serious adverse event (SAE) related to the IMP
4. Subject has not permanently discontinued the IMP

7.4. Prohibited Medications

The use of any other investigational drug except elamipretide is prohibited during the conduct of the current trial.

The concurrent use of sacubitril (an antihypertensive drug used in combination with valsartan marketed under the brand name, Entresto, in the US) is prohibited, due to a lack of current information regarding possible drug interactions.

All medications, including over-the-counter treatments, vitamins, or supplements, must have been stable, in the opinion of the Investigator, for at least 30 days prior to the Baseline Visit and is not planning on beginning new therapy during the trial. All concomitant medications will be recorded in the source data and the Electronic Case Report Form (eCRF). Changes in dosages of current medications (including over-the-counter vitamins or supplements) during the conduct of the trial will be discouraged, unless required to treat an Adverse Event.

Subjects will be instructed to maintain their normal diet, daily caffeine, and fiber intake throughout the trial period.

7.5. Discontinuations

7.5.1. Discontinuation of Subjects

Subjects may be discontinued for the following reasons:

- Investigator Decision
    - The Investigator decides that the subject should be discontinued from the trial for any reason.
- Subject Decision
    - The subject or the subject's designee, (e.g., parents or legal guardian), requests to be withdrawn from the trial.
        - Subjects who withdraw should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented.
        - Preferably the subject should withdraw consent in writing and, if the subject or the subject's representative refuses or is physically unavailable, the trial center should document and sign the reason for the subject's failure to withdraw consent in writing.
    - The subject is lost to follow-up after a reasonable number of attempts to contact the subject (including documented phone calls and/or emails, and a certified letter) have been completed.
- Sponsor Decision

  - The Sponsor or its designee stops the trial or stops the subject's participation in the trial for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

- Adverse Event
  - If the Investigator decides that the subject should be withdrawn because of an AE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately.

Any subject withdrawing from the trial will be asked to complete the Part 1 or Part 2 Early Discontinuation Visit assessments (Attachment 1), as appropriate.

7.5.2. Discontinuation of Trial Center

Trial center (research center) participation may be discontinued if the Sponsor or its designee, the Investigator, or the Ethics Committee (EC) of the trial center judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

7.5.3. Discontinuation of the Trial

The trial will be discontinued if the Sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

8. TREATMENT

8.1. Treatments Administered

This randomized, double-blind, placebo-controlled crossover trial followed by an open-label treatment extension assessment will enroll approximately 12 subjects who have genetically confirmed Barth Syndrome. Subjects will be randomized (1:1) to one of two sequence groups: 12-weeks of single daily subcutaneous (SC) doses of 40 mg elamipretide in Treatment Period 1 followed by 12-weeks of treatment with placebo in Treatment Period 2 (separated by 4-week washout period), or vice versa. Subjects who will continue into Part 2 will receive up to 168 weeks of single daily SC doses of 40 mg elamipretide. The Part 1 and Part 2 Trial Schematics are presented in Attachment 3. IMP may be administered daily to the subject in the abdomen (rotating around the four abdominal quadrants) or thigh, provided that it is at least 5 cm from the previous day's location of administration, by either a trained caregiver or the subject. Administration of IMP will occur at approximately the same time every day (e.g. early morning, noon, early afternoon, or evening) during each Treatment Period.

At the Treatment Period 1 Baseline and Treatment Period 2 Pre-dose Visits, IMP will be administered after completion of all specified procedures (Section 6.3.1.2.1 and Section 6.3.1.4.1). Subjects or caregivers will receive instruction on scheduling daily home (or other Investigator agreed upon location) visits with the Visiting Nurse and may be assigned a Visiting Nurse to administer IMP subcutaneously at the Treatment Period 1 Week 1, Week 4, and Week 8 Visiting Nurse Visits and Treatment Period 2 Week 1, Week 4, and Week 8 Visiting Nurse Visits. Subjects (or caregivers) will be trained on the procedure for administration of IMP and will administer IMP on a daily basis at approximately the same time each day (e.g. early morning, noon, early afternoon, or evening).

If, for any reason, a subject (or trained caregiver) is unable/unwilling to administer IMP, a Visiting Nurse or clinical site staff may administer IMP .

8.2. Materials and Supplies

IMP (elamipretide and placebo for Part 1 and only elamipretide for Part 2) will be dispensed, stored, and administered according to the Pharmacy Manual.

8.2.1. Elamipretide

Elamipretide drug product will be provided as a sterile solution for administration by SC injection. Additional details regarding the IMP will be provided in the Pharmacy Manual.

8.2.2. Placebo

Placebo will be provided as a sterile solution for administration by SC injection. Additional details regarding the IMP will be provided in the Pharmacy Manual.

8.3. Treatment Logistics and Accountability

All drug accountability records must be kept current, and the Investigator must be able to account for all used and unused vials of IMP. These records should contain the dates, quantity, and IMP:

- Received at trial center
- Administered to each subject
- Dispensed to each subject
- Returned from each subject
- Disposed of at the trial center or returned to the Sponsor or designee

The clinical monitor responsible for the trial center will provide written approval for the destruction or return of unused IMP vials following reconciliation of all clinical supplies.

8.4. Rationale for Selection of Doses in the Trial

Multiple clinical pharmacology studies have been conducted to date, to assess the safety, tolerability and PK of elamipretide and its metabolites. Two similarly designed trials (SPISC-101 and SPISC-102) have been conducted to evaluate the safety, tolerability and pharmacokinetics (PK) of single (2-80 mg) and 7-day repeat-dose administration (6-80 mg) of ascending doses of elamipretide administered subcutaneously (SC) to healthy volunteers. In these studies, elamipretide was associated with no systemic safety issues. Local injection site reactions were limited to transient, local erythema and occasional pruritus, pain, or swelling, which resolved spontaneously, generally within 4 hours post-dose, without sequelae.

The systemic exposure (in terms of mean $AUC_{0-\tau}$ on Day 7) to elamipretide following repeat SC injection at 40 mg in 1 mL was 3,810 ng·h/mL, while mean C_{max} on Day 7 was 1,320 ng/mL. No accumulation of elamipretide was seen following repeat dosing for seven consecutive days. Neither metabolite of elamipretide (M1 and M2) is active or implicated in toxicology.

The SPIMM-201 trial provides supporting information regarding safety and plasma exposure in the PMD population following repeat-dose administration of elamipretide at 0.01, 0.1, 0.25 mg/kg/hr as a 2-hour IV infusion (Total Daily Dose [TDD] 0.02, 0.2, 0.5 mg/kg) for 5 days. Elamipretide demonstrated an acceptable safety and tolerability profile. The primary efficacy endpoint (distance walked during the 6MWT) appeared to improve with increasing doses and the highest level of functional improvement was observed at 0.25 mg/kg/day, a TDD of 0.5 mg/kg/day. PK data is presented in Table 3.

Table 3: SPIMM-201: Mean Steady-State PK Parameters* on Day 5 (males and females combined) Following Repeat Administration of elamipretide (MTP-131) at 0.01, 0.1 and 0.25 mg/kg/hr as a 2-hour IV infusion, Once Daily, for 5 Days

Dose	Mean Body Weight of Dose Group (kg)	Mean Total Daily Dose (TDD) (mg)	Analyte	C_{max} (ng/mL) [n]	$AUC_{0\text{-last}}$ (ng.h/mL) [n]
0.01 mg/kg/hr given as a 2hr IV infusion	70.6	1.412	MTP-131	35.8 [n=7]	140 [n=6]
			M1	15 [n=7]	111 [n=7]
			M2	2.6 [n=7]	44 [n=6]
0.1 mg/kg/hr given as a 2hr IV infusion	63.7	12.74	MTP-131	498 [n=9]	1992 [n=5]
			M1	183 [n=9]	1672 [n=5]
			M2	39.6 [n=9]	661 [n=8]
0.25 mg/kg/hr given as a 2hr IV infusion	59.2	29.6	MTP-131	1050 [n=9]	4050 [n=7]
			M1	285 [n=9]	2190 [n=7]
			M2	68.8 [n=9]	1169 [n=8]

*Calculations based on nominal time points. Data is draft and QC'd.

Bioavailability for C_{max} and $AUC_{0\text{-last}}$ following administration of a TDD of 40 mg elamipretide as a two hour, IV infusion and as a single SC injection can be estimated by applying a correction factor to the IV parameters to normalize TDD to 40 mg (assumes proportionality of relationship between dose levels and exposure parameters for elamipretide, M1 and M2, as previously described) and deriving percentage exposures (Table 4).

Table 4: SPIMM-201: Estimated Bioavailability of SC administration (40 mg as a 1 mL injection) versus Two Hour IV Infusion Following Repeat Administration of elamipretide (MTP-131)

						PK Parameters following 40mg SC		**Estimated Bioavailability**	
Dose	Mean TDD (mg)	Correction factor for 40 mg TDD	Analyte	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng.h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng.h/mL)	**C_{max}**	**$AUC_{0\text{-last}}$**
0.25 mg/kg/hr given as a 2hr IV infusion	29.6	1.35	MTP-131	1418	5468	1,300	3,720	**92%**	**68%**
			M1	385	2957	436	3,100	**113%**	**105%**
			M2	92.9	1578	88.0	1,950	**95%**	**124%**

*Calculations based on nominal time points. Data is draft and QC'd.

Despite bioavailability of 68% (by $AUC_{0\text{-last}}$) when comparing the SC injection to the two-hour IV infusion, exposure to elamipretide by 40 mg SC injection will remain similar to or greater than exposure demonstrated in the SPIMM-201 trial in subjects weighing <80 kg therefore, treatment effect is not likely to be altered by the change in dose route.

To enable chronic dosing of elamipretide, chronic (26-weeks in rat, SPI-CIT-15-03; 39-weeks in dog, SPI-CIT-15-02) repeat-dose toxicology studies have been conducted to evaluate the systemic toxicity and local tolerability of elamipretide administered as SC injections, once

daily. No systemic toxicity was apparent at any elamipretide dose tested and the predominant trial findings were related to local injection site reactions and tolerability. Safety margin calculations for both non-clinical species, compared to the 40 mg/day (1 mL) SC dose in man are provided in Table 5.

Table 5: SPI-CIT-15-03, SPI-CIT-15-02: Key Summary Steady-state PK Parameters Days 182 (Rat) and 273 (Dog) at the NOAEL/MFD with Safety Margins vs. Human Exposure (SPISC-101, 40 mg/day)

					PK in Man Following 40mg SC		Safety Margin	
Trial / NOAEL	**Species**	**Analyte**	**C_{max} (ng/mL)**	**$AUC_{0\text{-last}}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**$AUC_{0\text{-last}}$ (ng.h/mL)**	**By C_{max}**	**By AUC**
SPI-CIT-15-03 15 mg/kg/day	Rat	MTP-131	6875	23,850	1,300	3,720	x5	x6
		M1	7385	43,000	436	3,100	x17	x14
		M2	260	2470	88.0	1,950	x3	x1.8
SPI-CIT-15-02 10 mg/kg/day	Dog	MTP-131	13050	21135	1,300	3,720	x10	x6
		M1	1709	5507	436	3,100	x4	x1.8
		M2	312	5093	88.0	1,950	x4	x3

The data displayed demonstrate that exposure to elamipretide, M1 and M2 in the chronic toxicology studies are supportive of chronic dosing at 40 mg/day by SC injection, in human, assuming an average body weight of approximately 75 kg and normal renal function (GFR > 90 mL/min).

The PK of elamipretide is body weight dependent. In a clinical pharmacology study assessing the safety and PK of elamipretide administered as SC injection, once daily for 7 days (SPISC-102), body weight plotted against C_{max} and $AUC_{0\text{-last}}$ of elamipretide and its' metabolites demonstrated negative correlation; as body weight increases, C_{max} and $AUC_{0\text{-last}}$ will decrease in an approximately linear manner. These data indicate that an individual with a body weight of 40 kg may be expected to have 25% greater exposure to elamipretide and M1 and 45% greater exposure to M2 than an individual with a body weight of 75 kg at the same dose level of study drug. Safety margins displayed in Table 3 demonstrate that an individual with a body weight of 30 kg administered 40 mg elamipretide SC would be expected to remain within acceptable ranges of exposure to elamipretide, M1 and M2 and are therefore included in the study population. Patients with body weight < 30 kg are excluded from participation.

Elamipretide and its' metabolites are excreted by the kidney, therefore decreased renal function impacts the PK of the compounds. A clinical pharmacology trial in subjects with normal renal function or mild, moderate or severe renal impairment (SPICP-101) demonstrates a negative correlation between GFR and exposure to elamipretide, M1 and M2; as GFR decreases C_{max} and $AUC_{0\text{-last}}$ will increase in an approximately linear manner. Exposure to elamipretide is expected to be approximately 2.3-fold higher in a subject with GFR < 30 mL/min compared to the corresponding exposure in a subject with normal renal function while M1 and M2 increase approximately 3.9-fold and 8.4-fold respectively in the same comparison. Safety margins displayed in Table 3 demonstrate that in order to maintain adequate toxicity exposure for dose levels in human, a dose level of 40 mg elamipretide SC would be expected to remain within acceptable ranges of exposure to elamipretide, M1 and M2 in subjects with GFR >60 mL/min,

assuming average body weight (75 kg). Subjects with GFR < 60 mL/min are excluded from participation.

Taken together, body weight and renal function effects on exposure of elamipretide and its' metabolites allow the following inclusion criteria in this study:

a. Patient body weight > 30 kg with GFR ≥ 90 mL/min/1.73 m^2 OR
b. Patient body weight > 40 kg with GFR ≥ 60 mL/min/1.73 m^2.

8.5. Treatment Compliance

During the treatment period, IMP will be administered daily by a trained caregiver or self-administration. In Part 1, a diary will be used to document administration.

8.6. Continued Access to Investigational Medicinal Product

Trial subjects may be eligible for an open-label extension trial following the conclusion of the trial.

8.7. Blinding and Unblinding Procedures

The trial personnel and subjects will be blinded to treatment until the database is locked.

The Investigator will contact the Sponsor prior to unblinding any subject's treatment sequence unless in the instance of a medical emergency.

In case of an immediate medical emergency or if directed by the Sponsor, and only if the information is required by the Investigator to manage a subject's AE, is a subject's treatment assignment to be unblinded prematurely. In cases of medical emergency, the Investigator may unblind a subject's treatment assignment using the computerized system according to the instructions received. The Sponsor must be notified as soon as possible regarding the reason for unblinding.

Whenever the treatment assignment of an individual subject is unblinded, the individual who performed the unblinding, the date, time and reason for the unblinding must be logged in the computerized unblinding system (IWRS) and also included in source documentation. The name of the individual who broke the blind must be included in the trial center's source documentation.

The Sponsor designated CRO will control and document, according to the appropriate Standard Operating Procedures, the disclosure of treatment assignments, and treatment identity. These procedures ensure that no blinded staff (CRO, trial center, Sponsor) will have premature access to the subjects' treatment assignments.

9. EFFICACY AND SAFETY EVALUATIONS AND APPROPRIATENESS OF MEASUREMENTS

Trial procedures and their timing are summarized in Attachment 1, Attachment 2, and Attachment 3.

9.1. Efficacy Endpoints

9.1.1. Primary Endpoints

- Distance walked (meters) during the 6-Minute Walk Test (6MWT)
- Total Fatigue on the BarTH Syndrome Symptom Assessment (BTHS-SA)
    - The Total Fatigue score on a given day is the sum of Q1 [tiredness at rest], Q2 [tiredness during activities], and Q4 [muscle weakness during activities]. The calculated value of the endpoint is the average of the 7 days prior to the office visit. If any of the 3 questions are not answered on any given day, then the Total Fatigue score for that day will be set to missing.

9.1.2. Secondary Endpoints

- Muscle strength as measured by handheld dynamometry (HHD)
- Five Times Sit-to-Stand Test score
- 2-D and 3-D Echocardiographic measurements
- Accelerometry counts
- SWAY Application Balance Assessment
- Patient reported outcomes
    - PROMIS Short Form Fatigue
    - Fatigue During Activities on the BTHS-SA
        - The Fatigue During Activities score on a given day is the sum of Q2 [tiredness during activities] and Q4 [muscle weakness during activities]. The calculated value of the endpoint is the average of the 7 days prior to the office visit. If either of the questions is not answered on any given day, then the Fatigue During Activities score for that day will be set to missing.
    - Patient Global Impression (PGI) Scales
        - PGI of Symptoms
        - PGI of Change
    - EQ-5D
- Clinician Global Impression (CGI) Scales

- CGI of Symptoms
- CGI of Change

- Caregiver Global Impression (CaGI) Scales
  - CaGI of Symptoms
  - CaGI of Change
- Biomarkers
  - MLCL: L4-CL Ratio
  - Plasma and blood biomarkers (GDF-15, FGF-21, glutathione/reduced glutathione)
  - Urine biomarkers (8-isoprostane, 8-hydroxy-2-deoxyguanosine, 3-methylgutaconic acid)
  - Plasma and urine metabolomics
  - Exploratory biomarkers

9.1.3. Pharmacokinetic (PK) Endpoints

Assessment of PK via a population model (see Section 11.2.6)

9.2. Safety Endpoints

The safety and tolerability endpoints will be assessed by:

- AEs
- Vital signs
- ECGs
- Ambulatory arrhythmias
- Clinical laboratory evaluations
- Columbia-Suicide Severity Rating Scale (C-SSRS)

The safety profile of elamipretide will be assessed through the recording, reporting, and analyzing of adverse events, clinical evaluations, and laboratory tests.

Comprehensive assessment of adverse events experienced by the subject will be performed from the time of the subject's signature of informed consent, throughout the course of the trial, and until the conclusion of the clinical trial's post treatment follow-up period.

Subjects must be seen by a physician or designee (an appropriately trained healthcare professional) at every trial visit and the evaluation must be documented. Trial center personnel will report any adverse event (AE), whether observed by the Investigator (or designee), or reported by the subject.

The Investigator is responsible for promptly documenting and reporting all AEs observed during the trial in the subject's eCRF and applicable forms. The reporting period for AEs is described in Section 9.10.2.

9.3. Adverse Events

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

9.4. Pre-Treatment Events

Untoward events and/or incidental diagnoses that occur prior to IMP administration are by definition, unrelated to the IMP and will be reported as such in the data listings. Pre-treatment events or incidental diagnoses will be recorded on the past medical history electronic case report form (eCRF). However, if a pre-treatment event is assessed by the Investigator as related to a trial procedure and/or meets seriousness criteria, it will be recorded as an AE on the AE eCRF, processed, and followed accordingly.

9.5. Baseline Medical Conditions

Baseline medical conditions, related or not related to the therapeutic area of interest/investigation, that worsen in severity or frequency during the trial in a way that is not consistent with natural disease progression, in the opinion of the Investigator, should be recorded and reported as AEs.

9.6. Medical and Surgical Procedures

Medical or surgical procedures (including hospitalizations) scheduled prior to signing the informed consent, but occurring during the trial should not be captured as AEs. The condition leading to the procedure should be listed in the medical history and the procedure should be captured on the concurrent procedures page. Medical or surgical procedures not scheduled prior to signing the informed consent should not be recorded as adverse events; the condition that led to the need to perform the medical or surgical procedure will be the AE or SAE and the procedure should be captured on the concurrent procedures page.

9.7. Abnormal Laboratory and Other Abnormal Investigational Findings

Abnormal laboratory findings or other objective measurements, deemed clinically significant by the Investigator should be reported as an AE.

When reporting an abnormal laboratory finding as an AE or SAE, the description of the abnormality, rather than the abnormal value itself, should be recorded. A clinical diagnosis should be reported if the Investigator believes the finding is consistent with a disease process.

9.8. Symptomatic Overdose

In the event of an overdose of trial medication, the Investigator should use clinical judgment in treating the signs and symptoms of the overdose. The signs and symptoms should be reported as AEs. Overdoses must be reported immediately to the trial Medical Monitor.

9.9. Serious Adverse Events (SAE)

A SAE is any AE that:

- Results in death.
- Is life-threatening. The term "life-threatening" refers to a situation in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Any non-serious AE that worsens and meets the criteria for an SAE should be reported as a new AE and as an SAE. The start date of the SAE should be the date the AE worsened to meet the criteria for a SAE.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate screen(s) of the subject's eCRF.

9.10. Recording of Adverse Events

Complete and accurate data on all AEs experienced for the duration of the reporting period (defined below) will be recorded on an ongoing basis on the Adverse Event Case Report Form (CRF). All SAEs must be reported using the trial specific SAE Report Form, in addition to the Adverse Event CRF.

It is important that each AE entry include a verbatim term along with, onset and resolution dates, severity, seriousness, relationship to the IMP, action taken with respect to the IMP, and its outcome.

Investigators should use the adverse event definitions provided in the above sections and should observe the following guidelines when completing the AE pages of the CRF:

- Whenever possible, recognized medical terms should be used to describe AEs rather than colloquialisms (for example, 'influenza' rather than 'flu'), and abbreviations should be avoided.
- Adverse events should be described using a specific clinical diagnosis, if this is available, rather than a list of signs or symptoms (for example, 'congestive heart failure' rather than 'dyspnea, rales and cyanosis'). However, signs/symptoms that are not associated with an identified disease or syndrome, or for which an overall diagnosis is not yet available, should be reported as individual AEs.
- Provisional diagnosis (e.g. "suspected Myocardial Infarction") is acceptable but should be followed up to a definite diagnosis if finally, available. Similarly, a fatal event with an unknown cause should be recorded as "Unknown"
- In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

9.10.1. Investigator Assessments

9.10.1.1. Severity

Severity, which is a description of the intensity of manifestation of the AE, is distinct from the regulatory definition of *seriousness*. The Investigator is required to grade the severity of each adverse event according to the following guidelines.

Investigators must assess the severity/intensity of adverse events according to the following qualitative toxicity scale:

Mild: Associated with no limitation of usual activities or only slight discomfort; generally not requiring alteration or cessation of IMP administration; and/or not needing therapeutic intervention.

Moderate: Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of IMP administration; and/or requiring therapeutic intervention.

Severe: Associated with inability of subject to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

9.10.1.2. Relationship to the Investigational Medicinal Product (IMP)

Investigators must systematically assess the causal relationship of AEs to the IMP(s) according to the following guidelines:

Probable: A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the IMP, the event is unlikely to be attributed to underlying/concurrent disease, other drugs, or other factors, and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the IMP.

Unlikely: A causal relationship is improbable and/or another documented cause of the AE is most plausible.

Unrelated: A causal relationship is clinically/biologically improbable, there is not a plausible time sequence between onset of the AE and administration of the IMP, the event is likely to be attributed to underlying/concurrent disease, other drugs, or other factors, and there is no reasonable response on withdrawal.

9.10.1.3. Outcome of an Adverse Event

Investigators must follow all AEs and SAEs as described in Section 9.10.2. Outcome is defined as:

- Recovered/Resolved;
- Recovering/Resolving
- Not recovered/Not resolved
- Recovered/Resolved with sequelae;
- Fatal; or
- Unknown.

9.10.1.4. Reporting of Injection Site Reactions (ISR)

Local ISRs have been frequently experienced with SC elamipretide administration. Characteristics of these injection site reactions were mild erythema, mild swelling, and mild pruritus, commencing within the first hour of the injection and generally resolving within 4 hours.

In order to standardize the reporting of ISRs, the following guidance should be followed:

- Any ISR following SC administration should be reported as an AE.
    - The ISR should be assessed for severity using the "Table for Grading the Severity of Site Reactions to Injections" provided in Attachment 16.
    - Any ISR that meets any of the criteria of an SAE (Section 9.9) should be reported within 24 hours of the study center first becoming aware of the event (as outlined in Section 9.11).
    - The ISR should be reported as the characteristic of the ISR, rather than the general term of "Injection Site Reaction". For instance, erythema associated with an ISR should be reported as "injection site erythema" or "redness at injection site" rather than the broad term "injection site reaction".

- For ISRs which reoccur following a subsequent SC injection, only one event should be recorded on the eCRF, with the overall duration to include the start date of the first reported event and the end date of the last recurrent event. The severity grade should be the most severe of the recurrent event during this period.

9.10.2. Adverse Event Reporting Period

The adverse event reporting period begins when the subject signs the informed consent and continues through the clinical trial's post treatment follow-up period.

After trial completion, all SAEs with an ongoing/unknown outcome will be followed-up until resolution or stabilization. Additional information on SAEs, obtained after database lock, will reside solely in the safety database.

9.11. Serious Adverse Event Expedited Reporting

In the event of a SAE occurring during the reporting period, the Investigator must immediately (within 24 HOURS after becoming aware of the SAE) inform the Sponsor by telephone, by fax or by e-mail as detailed in the SAE form, completion instructions, CRF completion guidelines, and/or Safety Management Plan.

For any SAE, the following minimum information is required as initial notification:

- Investigator/Reporter with full contact information
- Subject identification details (trial number, center number, subject number),
- IMP administration details (dose and dates)
- Event Verbatim, a brief description of signs/symptoms/or diagnosis and the date of onset,
- Seriousness criteria (ion) met, and,
- Relationship of the event to the IMP (e.g., the causality according to the Investigator)

All SAE reports should be transmitted according to the Safety Management Plan.

The Investigator/Reporter must provide follow-up information as available or requested by the Sponsor.

9.11.1. Pregnancy and Contraception

For male subjects with female partners of child-bearing potential, highly effective methods of contraception must be adhered to prior to entry into the study and for at least 2 months after last dose of study drug. Highly effective methods of contraception is defined as the usage by the female partner of any form of hormonal contraception or intra-uterine device (which should be established prior to the start of the study) plus usage by one of the partners of an additional spermicide-containing barrier method of contraception. Male subjects with pregnant partners must use a condom with spermicide from the start of treatment until at least 2 months after the

last dose of study drug. Sperm or egg donation by subjects is not permitted from the start of treatment until 2 months after the study drug was administered.

Any pregnancy in a female partner of a male subject during the course of the trial and until the last follow-up visit must be reported within 24 hours of learning of the pregnancy even if no AE has occurred, as detailed in the Safety Management Plan. If the investigator suspects the pregnancy has resulted from an interaction of the trial medication with contraceptives, then the pregnancy is considered as an AE; however, all pregnancies must be recorded in the AE page/section of the CRF.

Investigators must actively follow up, document, and report on the outcome of every pregnancy, even if the subject is withdrawn from the trial, as detailed in the Safety Management Plan.

9.11.2. Responsibilities to Regulatory Authorities, Investigators and Ethics Committees

The Sponsor will send appropriate safety notifications to regulatory authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable center-specific requirements related to the reporting of SAEs involving his/her subjects to the Ethics Committee/Institutional Review Board (EC/IRB) that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the EC's/IRB's approval/favorable opinion to continue the trial. In particular, and in line with respective regulations, the Sponsor will inform the Investigator of adverse events that are both serious and unexpected and are considered to be related to the administered IMP ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of these Safety reports in the Investigator Site File. National regulations with regard to Safety report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety reports directly to the concerned lead IEC/central IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or center-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that Directive and with the related detailed Guidances.

9.12. Appropriateness of Measurements

The measures used to assess safety in this trial are consistent with those widely used and generally recognized as reliable, accurate, and relevant.

10. DATA QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the trial centers, as appropriate
- Sponsor start-up training to instruct the Investigators and trial coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and trial procedures.
- Make periodic visits to the trial center
- Be available for consultation and stay in contact with the trial center personnel by mail, telephone, and/or fax
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- Conduct a quality review of the database

In addition, the Sponsor or its representatives will periodically check a sample of the subject data recorded against source documents at the trial center. The trial may be audited by the Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the trial, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the trial. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable ECs with direct access to original source documents.

10.1. Data Capture System

An electronic data capture system (eDC) will be used in this trial. The trial center will maintain a separate source for the data entered by the trial center into the Sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, or any data for which electronic documentation is provided by the subject, will be stored electronically in the central vendor's database system.

Any data for which paper documentation provided by the subject will serve as a source document will be identified and documented by each trial center in that center's trial file. Paper documentation provided by the subject may include, for example, a paper diary to collect subject reported outcome measures (e.g., a rating scale), a daily dosing schedule, or an event diary.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

For this Phase 2, randomized, double-blind, placebo-controlled crossover trial followed by an open-label treatment extension assessment, a sample size of approximately 12 subjects is planned. Assuming an underlying standard deviation of paired differences of 50 meters for the 6MWT distance and 1.3 points for the BTHS-SA Total Fatigue score, 12 subjects provides for nearly 80% power to detect a mean improvement of 50 meters in the 6MWT or 1.3 points for the BTHS-SA Total Fatigue score, with each potentially tested at the 0.025 (two-sided) level of significance (associated with a potential adjustment via Hochberg's procedure). Subject numbers are restricted by feasibility considerations (availability of subjects) but that recruitment could be greater if subjects are available (up to 16 subjects).

11.2. Statistical and Analytical Plans

11.2.1. General Considerations

All trial data are to be displayed in the data listings.

Statistical analysis of this trial will be the responsibility of the Sponsor or its designee.

Additional details regarding analyses will be included in separate statistical analysis plan (SAP).

11.2.2. Subject Disposition

All subjects who discontinue from the trial will be identified, and the extent of their participation in the trial will be reported. If known, a reason for their discontinuation will be given.

11.2.3. Subject Characteristics

Subject's age, sex, weight, height, body mass index (BMI), and other demographic characteristics will be recorded and summarized.

Medical history will be listed.

11.2.4. Endpoints and Methodology

11.2.4.1. General Considerations

Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minima, and maxima) for continuous variables and using frequencies and percentages for discrete variables. Data will be presented by treatment group as appropriate, where treatment is defined for subjects within a specific period. Formal statistical tests (where performed) will be 2-sided at the alpha=0.05 level of significance, except where otherwise noted to adjust for multiplicity for the primary endpoint family.

11.2.4.2. Analysis Populations

Approximately 12 subjects will be randomized and will receive either IMP (elamipretide or placebo) in the first treatment period, followed by the alternative treatment in the second treatment period, according to the randomly assigned treatment sequence.

Statistical analysis will be performed in the following populations:

Safety Population – Includes all trial subjects who receive at least 1 dose of IMP according to treatment received within a period.

Intention-to-Treat (ITT) Population – Includes all trial subjects who receive at least 1 dose of IMP, according to the treatment sequence group to which they were randomized.

Per-Protocol (PP) Population – Includes all ITT subjects without major protocol violations/deviations. The list of major protocol violations/deviations will be identified and specified prior to final database lock for the trial that would lead to exclusion for the PP analysis.

Pharmacokinetic (PK) Population – Includes all trial subjects who have at least 1 PK sample taken during their participation.

The details of all analyses will be described in the Statistical Analysis Plan to be finalized before unblinding.

11.2.5. Efficacy Analyses

Efficacy analyses will be conducted on the ITT population. All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05.

The distance walked (meters) during the 6MWT and Total Fatigue score on the BTHS-SA constitute the family of primary endpoints. A family-wise alpha level of 0.05 will be maintained for the primary endpoint family, using Hochberg's procedure. If both primary endpoints are significantly different from placebo at the 0.05 (two-sided) level of significance (in favor of treatment), then both will be considered statistically significant. Otherwise the endpoint with the smaller p-value of the two will be considered statistically significant, if statistically significant at the 0.025 (two-sided) level of significance.

Analyses of continuous endpoints at the end of each treatment period will be conducted utilizing a mixed model repeated measures (MMRM) approach. Subject will be considered as a random effect. Additional details regarding the model and underlying assumptions will be specified in the SAP.

Secondary and exploratory efficacy endpoints will be assessed in a similar manner as the primary efficacy endpoints.

No adjustments for multiplicity will be provided for secondary or exploratory endpoints.

11.2.5.1. Handling of Missing Data

A significant amount of missing data are not anticipated, given characteristics of the subject population from which subjects will be enrolled. In addition, the mixed model repeated measures approach is valid under a missing at random (MAR) missingness mechanism.

Nevertheless, depending on the extent of missing data, additional sensitivity analyses may be considered.

11.2.6. Pharmacokinetic (PK) Analysis

Elamipretide and metabolite plasma concentration data will be collected in all subjects and will be used in a non-linear mixed effects model to assess the characteristics of elamipretide and metabolite PK in the PK population.

The PK model will be generated and validated using data reported from historical, thorough PK studies. Where sufficient data allows, covariates will include age, race, renal function (as described by eGFR), intercurrent conditions and concomitant medications.

Plasma samples will be analyzed for elamipretide and metabolites using a validated liquid chromatography/ tandem mass spectrometry assay.

Additional details and all model assumptions, validation and data analysis will be detailed in the PK Analysis Plan prior to database lock.

11.2.7. Safety Analyses

Safety data analysis will be conducted on all subjects in the Safety Population with treatment group determined by treatment received in a particular period (i.e., subjects dosing in both periods will be counted in both treatment groups).

11.2.7.1. Adverse Events

The number and percentage of subjects experiencing 1 or more AEs will be summarized by treatment group, relationship to IMP, and severity. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs will be summarized by system organ class (SOC), preferred term (PT), and treatment group.

All reported AEs will be listed, but only treatment-emergent adverse events (TEAEs) will be summarized.

The incidence of all TEAEs, drug relationship with TEAEs, and severity of TEAE will be summarized. In the summary tables, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once (within a treatment group). If a subject has the same AE on multiple occasions (with a treatment period), the highest severity (severe > moderate > mild) or drug relationship (probable > possibly related > unlikely related > unrelated) recorded for the event will be presented. If severity is missing, subjects will be included as missing (for severity). If drug relationship is missing, subjects will be included in related tables (e.g., considered related).

11.2.7.2. Deaths and Other Serious Adverse Events

Listings will be provided for the following:

- Deaths
- SAEs

- AEs leading to discontinuation of IMP

11.2.7.3. Clinical Laboratory Evaluations

Summary tables for laboratory parameters (including hematology, chemistry, and urinalysis) will include descriptive statistics of change relative to baseline where appropriate, and data listings of clinically significant abnormalities.

Subjects with laboratory data outside the normal range will be listed with abnormal values flagged.

Shift tables (e.g., tables that show the number of subjects who are low, normal, or high at baseline versus each post-baseline scheduled assessment) will be produced.

The number and percentage of subjects with urinalysis results outside the normal range will be presented by endpoint and visit for each treatment group. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of trial.

11.2.7.4. Vital Signs

Vital signs data will be summarized by changes from baseline values at each treatment group using descriptive statistics.

Shift tables for heart rate and blood pressure (e.g., tables that show the number of subjects who are low, normal, or high at baseline versus each post-baseline scheduled assessment) will be produced.

11.2.7.5. Electrocardiogram

ECG data will be summarized by changes from baseline values at each treatment group using descriptive statistics.

Electrocardiogram results (normal versus abnormal) and an assessment of the clinical significance of any abnormalities, in the opinion of the Investigator, will be listed for individual subjects. Intervals of PR, RR, QRS, QT, and QTcB will also be listed.

Similar data will be reported for ambulatory arrhythmias.

11.2.7.6. Other Safety Parameters

Any other safety data captured on the eCRF will be listed.

12. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

12.1. Informed Consent

The Investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the trial, including answering any questions the subject may have throughout the trial and sharing in a timely manner any new information that may be relevant to the subject willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of trial participation to the subject in simple terms before the subject is entered into the trial, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the trial and desires to participate in the trial.

The Investigator is responsible for ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

As used in this protocol, the term "informed consent" includes all consent and assent given by subject or their legal representatives.

12.2. Ethical Review

The Sponsor or its representatives must approve all ICFs before they are used at investigative trial center. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of EC approval of the protocol and the ICF must be provided to the Sponsor before the trial may begin at the investigative trial center. The EC will review the protocol as required.

The trial center's EC should be provided with the following:

- The current IB and updates during the course of the trial
- ICF
- Relevant curricula vitae

12.3. Regulatory Considerations

This trial will be conducted in accordance with:

1) Consensus ethics principles derived from international ethics guidelines, including the CIOMS International Ethical Guidelines
2) The ICH GCP Guideline [E6]
3) Applicable laws and regulations

The Investigator or designee will promptly submit the protocol to applicable EC(s). Some of the obligations of the Sponsor may be assigned to a third-party organization.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data.

12.3.1. Protocol Approval

The Sponsor's responsible medical officer will approve the protocol, confirming that, to the best of their knowledge, the protocol accurately describes the planned design and conduct of the trial.

12.3.2. Final Report Approval

The Sponsor's responsible medical officer will approve the final clinical trial report for this trial, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the trial.

12.3.3. Trial Monitoring

The Investigators and institution(s) will permit trial-related monitoring of the CRF data by Stealth BioTherapeutics, Inc., or their assignee by providing direct access to source data and/or documents. The trial monitor will verify the eCRFs 100% against the source documentation. Deviations from the protocol with regard to subject enrollment or trial conduct will also be noted in the source documentation, in the eCRF and a complementary database. A Sponsor representative will visit the trial center to initiate the trial, prior to the first treatment of the first subject, and at agreed times throughout the trial, including at the end of the trial. Drug dispensing and clinical drug supply records will be 100% verified at the trial center by the trial monitor. It is understood that all subject specific information is confidential and no documentation that can link trial information to the specific subject will be collected or retained by the Sponsor.

12.3.4. Retention of Records

All trial related material including source documents, eCRFs, Central Authority, and EC correspondence and analyses and any other documentation required by applicable laws and regulations will be maintained for 15 years after completion of the trial or notification from the Sponsor that the data can be destroyed, whichever comes first.

12.3.5. Disclosure of Information

Information concerning the investigational medication and patent application processes, scientific data or other pertinent information is confidential and remains the property of Stealth BioTherapeutics, Inc. The Investigator may use this information for the purposes of the trial only. It is understood by the Investigator that Stealth BioTherapeutics, Inc., will use information developed in this clinical trial in connection with the development of the investigational medication and therefore may disclose it as required to other clinical Investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical trial, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this trial to the Sponsor.

The Investigator may not submit for publication or presentation the results of this trial without first receiving written authorization from Stealth BioTherapeutics, Inc. Stealth BioTherapeutics, Inc., agrees that before it publishes any results of the trial, it shall provide the Investigator with at least 30 days for review of the pre-publication manuscript prior to the submission of the manuscript to the publisher.

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14. ATTACHMENTS

Attachment 1 Part 1 and Part 2 Schedule of Assessments (Trial Center Visits)

Part 1	**Screening [a]**	**Treatment Period**				
Treatment Period 1[b]	**Day -28 to Day -1 (min. approx. 7 days)**	**Visit 1 Pre-dose (Baseline) Visit[c] (Day 1)**	**Days 2-5 Visits[d]**	**Visit 5 Week 12 Visit (Day 85 ± 7)**	**Washout Period[e] (28 days +7)**	
Treatment Period 2[b]		**Visit 6 Pre-dose Visit[c] (Day 1)**	**Days 2-5 Visits[d]**	**Visit 10 Week 12 Visit (Day 85 ± 7)**	**Part 1 Follow-up Period[e] (28 days +7)**	**Visit 11A Part 1 End-of-Trial/ Early D/C Visit[e] (Day 113 +7)**
Informed Consent	X					
Demographics	X					
Randomization[f]		X				
Review of Inclusion/Exclusion Criteria[f]	X	X				
Relevant Medical History[f]	X	X				
Concomitant Medication/Procedure Review	X	X		X		X
Review AEs		X	X	X	X	X
Physical Exam[g]	X	X		X		X
Vital Signs[h]	X	X		X		X
12-Lead ECG[i]	X	X		X		X
Blood Chemistry & Hematology[j]	X	X		X		X
Urinalysis[j]	X	X		X		X
Blood Spot[j]	X	X		X		X
Plasma and Urine Biomarkers[j]	X	X		X		X
Plasma and Urine Metabolomic Profile		X		X		X
2-D and 3-D Echos	X	X		X		X
AVIVO™ MPM System[k]	X	X		X		
C-SSRS "Lifetime Recent"	X					
C-SSRS "Since Last Visit"		X		X		X
PROMIS Short Form Fatigue[l]	X	X		X		X
BTHS-SA[m]	X----------Daily----------X					
PGI Scales[n]	X	X		X		X
CGI Scales	X	X		X		X
CaGI Scales[o]	X	X		X		X
EQ-5D[p]	X	X		X		X
6MWT[q]	X	X		X		X
5XSST[q]	X	X		X		X
HHD[q]	X	X		X		X
SWAY[q]	X	X		X		X
Daily IMP Injection[r]		X----------Daily----------X				

a. The ICF must be signed prior to any trial related procedures are performed. If applicable, informed consent in writing from parent(s) or legally-acceptable representative(s) and, informed assent from subject (if age appropriate according to local

requirements) should be provided.

b. All study center visits should occur at approximately (±2 hours) the same time and after at least 3 hours of fasting. Days and Weeks are relative to the Pre-dose Visit of the respective Treatment Period.
c. Screening assessments that were completed within 24 hours of the Baseline Visit, do not need to be recompleted. Pre-dose assessments must be completed within 24 hours prior to receiving IMP.
d. Subjects may be evaluated at the trial center daily for up to the first 5 days of each Treatment Period. The decision to have a subject return for the Days 2 through 5 Visits for both Treatment Period 1 and Treatment Period 2 should be made and documented prior to the Baseline Visit.
e. The Washout Period will only occur after Treatment Period 1. The Part 1 Follow-Up Period and the Part 1 End-of-Trial Visit will only occur after Treatment Period 2 and if the subject is not continuing into Part 2.
f. Only to be completed at the Baseline Visit.
g. Height will be measured during all physical examinations, and used in the trial to calculate BMI. Physical examination will include: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system, and weight.
h. Vital signs will include HR, RR, and BP after sitting for 5 min, and temperature.
i. All scheduled ECGs must be performed after the subject has rested quietly for at least 10 min in the supine position.
j. See Attachment 4 for laboratory tests. Additional blood samples, at the Treatment Period 1 Baseline Visit, Treatment Period 2 Week 12 Visit, and (if applicable) the Part 1 Early Discontinuation Visit, will be collected and stored for assessing the immunogenicity potential of the IMP.
k. Starting at the Screening Visit, subjects will be provided with an AVIVO™ MPM System which will be applied, as instructed in the product manual, at trial center visits by the Investigator (or designee). The Investigator (or designee) will educate the subject on appropriate application and use of the AVIVO™ MPM System. Subjects will be instructed and reminded to apply and wear a new AVIVO™ MPM System at approximately Week 11, immediately prior to the Treatment Period 1 Week 12 Visit and Treatment Period 2 Week 12 Visit. Subjects will be instructed to wear each AVIVO™ MPM System for approximately 7 consecutive days after each application. Subjects will return all AVIVO™ MPM Systems by the completion of his/her participation in the trial.
l. For subjects ≥ 18 years of age at the Screening Visit, the PROMIS Adult Short Form Fatigue should be completed. Subjects 12-17 years of age at the Screening Visit, the PROMIS Pediatric Short Form Fatigue should be completed for the duration of the trial.
m. The age appropriate BTHS-SA should be completed daily by the subject in a diary starting at the Screening Visit and continued until the Treatment Period 2 Week 12 Visit. For subjects ≥ 16 years of age at the Screening Visit, the BTHS-SA Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the BTHS-SA Adolescent should be completed for the duration of the trial.
n. For subjects ≥ 16 years of age at the Screening Visit, the PGI Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the PGI Adolescent should be completed for the duration of the trial.
o. If applicable. For subjects ≥ 16 years of age at the Screening Visit, the CaGI Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the CaGI Adolescent should be completed for the duration of the trial.
p. For subjects ≥ 16 years of age at the Screening Visit, the EQ-5D-5L should be completed. Subjects 12-15 years of age at the Screening Visit, the EQ-5D-Y should be completed for the duration of the trial.
q. The 6MWT (Attachment 14), the 5XSST (Attachment 15), and HHD should be performed after all other trial procedures (except for IMP administration). The 5XSST should be performed after the 6MWT and after at least 5 minutes rest (should not be more than 30 minutes). Handheld dynamometry should be performed after completion of the 5XSST and at least 5 minutes rest (should not be more than 30 minutes). The SWAY Application Balance Assessments should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes). The Investigator (or designee) conducting the 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should not be the same Investigator (or designee) completing the safety assessments for a particular subject.
r. At Treatment Period 1 and Treatment Period 2 Pre-dose Visits, all other trial procedures must be completed prior to administering IMP. Subjects should be instructed to administer the IMP on the day of Treatment Period 1 Week 12 and Treatment Period 2 Week 12 Visit, prior to returning to the trial center. The location (injection in the abdomen [rotating around the four abdominal quadrants] or thigh, provided that it is at least 5 cm from the previous day's location of administration]) and time of the IMP administration (at approximately the same time each day [e.g. early morning, noon, early afternoon, or evening]) will be recorded daily in a diary.

Part 2 (begins on the day after the Treatment Period 2 Week 12 Visit of Part 1)	**Treatment Period[a]**			**Part 2 Follow-Up Period**
Part 2 Treatment Period Visit	**Visit 11B (Week 12 Visit)**	**Visits 12-19 (Week 24, 36, 48, 72, 96, 120, 144, 168 Visits)**	**Phone Call (or other method) (Weeks 60, 84, 108, 132, 156)**	**Visit 20 (Week 172) Part 2 End-of-Trial or Early D/C Visit**
Window	**± 1 week**	**± 2 weeks**	**± 2 weeks**	**+ 7 days**
Concomitant Medication/Procedure Review	X	X	X	X
Review AEs	X	X	X	X
Physical Exam[b]	X	X		X
Vital Signs[c]	X	X		X
12-Lead ECG[d]	X	X		X
Blood Chemistry & Hematology[e]	X	X		X
Urinalysis[e]	X	X		X
Blood Spot[e]	X	X		X
Plasma and Urine Biomarkers[e]	X	X		X
Plasma and Urine Metabolomic Profile	X	X		X
2-D and 3-D Echos	X	X		X
C-SSRS "Since Last Visit"	X	X		X
PROMIS Short Form Fatigue[f]	X	X		X
BTHS-SA[g]	X	X		X
PGI Scales[h]	X	X		X
CGI Scales	X	X		X
CaGI Scales[i]	X	X		X
EQ-5D[j]	X	X		X
6MWT[k]	X	X		X
5XSST[k]	X	X		X
HHD[k]	X	X		X
SWAY[k]	X	X		X
PK Samples[l]	X			
Daily IMP Injection[m]	X----------Daily----------X			

a. All study center visits should occur at approximately (±2 hours) the same time and after at least 3 hours of fasting. Days and Weeks are relative to the Pre-dose Visit of the respective Treatment Period.
b. Height will only be measured during all physical examinations, and used in the trial to calculate BMI. Physical examination will include: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system, and weight.
c. Vital signs will include HR, RR, and BP after sitting for 5 min, and temperature.
d. All scheduled ECGs must be performed after the subject has rested quietly for at least 10 min in the supine position.
e. See Attachment 4 for laboratory tests. Additional blood samples, at the Part 2 Early Discontinuation Visit (if applicable), will be collected and stored for assessing the immunogenicity potential of the IMP.
f. For subjects ≥ 18 years of age at the Screening Visit, the PROMIS Adult Short Form Fatigue should be completed. Subjects 12-17 years of age at the Screening Visit, the PROMIS Pediatric Short Form Fatigue should be completed for the duration of the trial.
g. The age appropriate BTHS-SA should be completed only at clinical site visits. For subjects ≥ 16 years of age at the Screening Visit, the BTHS-SA Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the BTHS-SA Adolescent should be completed for the duration of the trial.
h. For subjects ≥ 16 years of age at the Screening Visit, the PGI Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the PGI Adolescent should be completed for the duration of the trial.
i. If applicable. For subjects ≥ 16 years of age at the Screening Visit, the CaGI Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the CaGI Adolescent should be completed for the duration of the trial.
j. For subjects ≥ 16 years of age at the Screening Visit, the EQ-5D-5L should be completed. Subjects 12-15 years of age at the Screening Visit, the EQ-5D-Y should be completed for the duration of the trial.
k. The 6MWT (Attachment 14), the 5XSST (Attachment 15), and HHD should be performed after all other trial procedures (except

for IMP administration). The 5XSST should be performed after the 6MWT and after at least 5 minutes rest (should not be more than 30 minutes). Handheld dynamometry should be performed after completion of the 5XSST and at least 5 minutes rest (should not be more than 30 minutes). The SWAY Application Balance Assessments should be performed after completion of the HHD and at least 5 minutes rest (should not be more than 30 minutes). The Investigator (or designee) conducting the 6MWT, 5XSST, HHD, and SWAY Application Balance Assessments should not be the same Investigator (or designee) completing the safety assessments for a particular subject.

l. PK Schedule: Pre-dose (-30 min); 0.5h (± 5 min); 1h (± 10 min); 2h (± 15 min); 4h (± 15 min). All PK sampling should be conducted at the defined time points at a single clinical site visit. The clinical site visit at which the PK sampling should occur should be the earliest clinical site visit possible in Part 2 (at or after the Week 12 Visit in Part 2). On the day of the Visit that the PK samples are collected, subjects should be instructed to administer the IMP at the trial center. To reduce trial procedure burden, PK sampling may be completed during a scheduled clinical site visits in Part 2 or on an independent clinical site visit. Additionally, to reduce the need for multiple venipunctures, in the opinion of the Investigator, a venous catheter may be used for PK sample collection.

m. Daily IMP injections should begin the day after the Part 1 Treatment Period 2 Week 12 Visit. On the day of the Visit that the PK samples are collected, subjects should be instructed to administer the IMP at the trial center. Injections should be in the abdomen (rotating around the four abdominal quadrants) or thigh, provided that it is at least 5 cm from the previous day's location of administration at approximately the same time each day (e.g. early morning, noon, early afternoon, or evening).

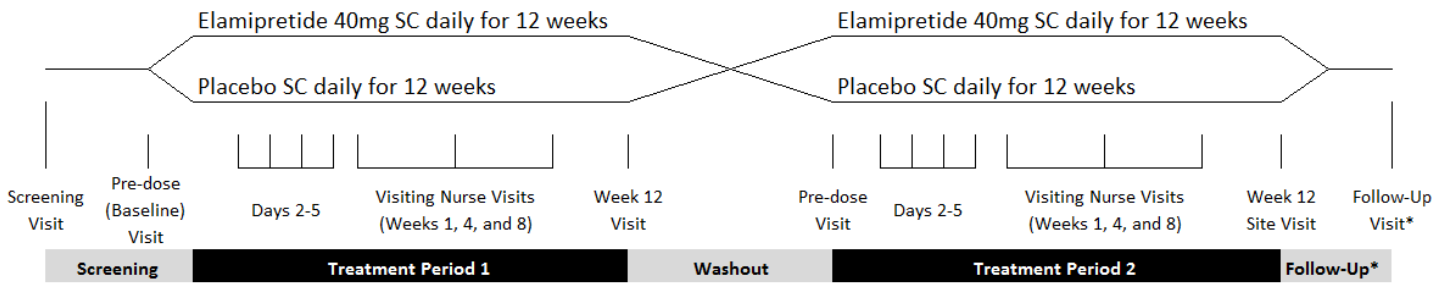
Attachment 2 Part 1 Schedule of Visiting Nurse Visit Assessments[a]

Treatment Period 1	Visit 2 Week 1 (Day 8 ± 1)	Visit 3 Week 4 (Day 29 ± 2)	Visit 4 Week 8 (Day 57 ± 2)
Treatment Period 2	**Visit 7 Week 1 (Day 8 ± 1)**	**Visit 8 Week 4 (Day 29 ± 2)**	**Visit 9 Week 8 (Day 57 ± 2)**
Confirm IMP storage conditions	X	X	X
IMP administration[b]	X	X	X
Injection site assessment[c]	X	X	X
Review AEs	X	X	X
Vital signs[d]	X	X	X
Clinical chemistry & hematology[e]	X	X	X
Plasma and urine biomarkers[e]	X	X	X
Reminder of new AVIVO™ MPM System[f]			X
PROMIS Short Form Fatigue[g]	X	X	X
BTHS-SA[h]	X----------Daily----------X		
PGI Scales[i]	X	X	X
CaGI Scales[j]	X	X	X
EQ-5D[k]	X	X	X
Review IMP compliance[l]	X	X	X

a. Given the challenges of scheduling Visiting Nurse Visits to subject's homes (or other Investigator agreed upon location) (e.g. remote geographic locations, subject scheduling conflicts, extreme weather or other natural disasters etc.), in consultation and agreement with the Sponsor and Investigator, these visits may be postponed, changed or cancelled. The decision on the schedule of Visiting Nursing Visits for both Treatment Period 1 and Treatment Period 2 should be made and documented prior to the Baseline Visit.
b. Visiting Nurse may administer IMP at all home (or other Investigator agreed upon location) visits.
c. Injection sites will be assessed using the "Table for Grading the Severity of Site Reactions to Injections" (Attachment 16). Completed forms will be sent to the study center for review.
d. Vital signs will include HR, RR, and BP after sitting for 5 min, and temperature.
e. See Attachment 4 for clinical laboratory tests.
f. Subjects will be reminded to apply and wear a new AVIVO™ MPM System for approximately 7 consecutive days immediately prior to the Treatment Period 1 Week 12 Visit and Treatment Period 2 Week 12 Visit.
g. For subjects ≥ 18 years of age at the Screening Visit, the PROMIS Adult Short Form Fatigue should be completed. Subjects 12-17 years of age at the Screening Visit, the PROMIS Pediatric Short Form Fatigue should be completed for the duration of the trial.
h. The age appropriate BTHS-SA should be completed daily by the subject in a diary starting at the Screening Visit and continued until the Treatment Period 2 Week 12 Visit. For subjects ≥ 16 years of age at the Screening Visit, the BTHS-SA Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the BTHS-SA Adolescent should be completed for the duration of the trial.
i. For subjects ≥ 16 years of age at the Screening Visit, the PGI Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the PGI Adolescent should be completed for the duration of the trial.
j. If applicable. For subjects ≥ 16 years of age at the Screening Visit, the CaGI Adult should be completed. Subjects 12-15 years of age at the Screening Visit, the CaGI Adolescent should be completed for the duration of the trial.
k. For subjects ≥ 16 years of age at the Screening Visit, the EQ-5D-5L should be completed. Subjects 12-15 years of age at the Screening Visit, the EQ-5D-Y should be completed for the duration of the trial.
l. The Visiting Nurse will assess compliance with IMP administration and may re-train the subject or caregiver on proper administration technique, as appropriate.

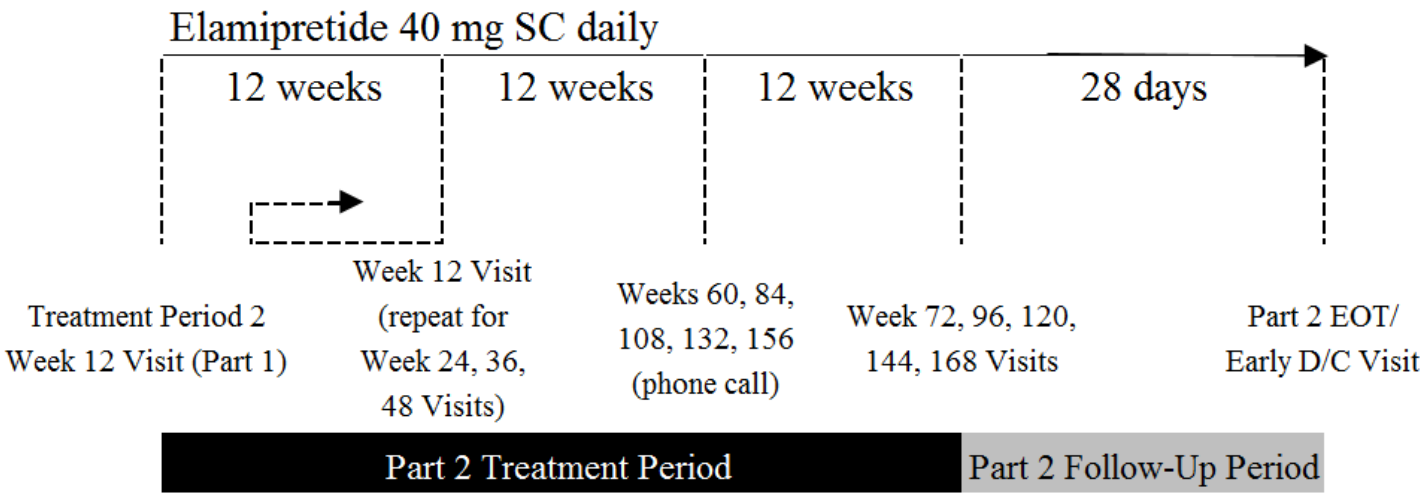
Attachment 3 Trial Schematics

Part 1



*only applicable if subject and/or Investigator decide not to continue subject into Part 2

Part 2



Attachment 4 Clinical Laboratory Tests

Haematology:	**Serum Clinical Chemistry:**
Haemoglobin	Sodium
Haematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Leukocytes (WBC)	Direct bilirubin
Neutrophils (ANC, segmented %)	Alkaline phosphatase (ALK-P)
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Gamma-glutamyl transpeptidase (GGTP)
Platelets	Creatine kinase (CK)
	Creatinine
Blood Spot	Calcium
MLCL: L4-CL Ratio	Glucose (non-fasting)
	Albumin
Biomarkers	Chloride
Serum GDF-15	Triglycerides
Serum FGF-21	HDL
Serum glutathione/reduced glutathione	LDL
Urine 8-hydroxy-2-deoxyguanosine	NT-proBNP
Urine 8-isoprostane	hs-Troponin I
Urine and plasma metabolomics (urine at site visits only)	
Urine 3-methylgutaconic acid	**Urinalysis**:
Immunogenicity (at Treatment Period 1 Baseline Visit, Treatment Period 2 Week 12 Visit, and [if applicable] Part 1 or Part 2 Early Discontinuation Visits only)	Specific Gravity
Exploratory biomarkers – to be determined by Sponsor (i.e. glial fibrillary acidic protein [GFAP] and Brain-Derived Neurotrophic [BDNF], ST2, Galectin-3 [GAL3], cystatin C and neutrophil gelatinase-associated lipocalin [NGAL])	pH
	Protein
	Glucose
	Ketones
	Blood
	Leukocyte esterase

Attachment 5 Columbia-Suicide Severity Rating Scale (C-SSRS) "Lifetime Recent"

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Lifetime Recent - Clinical

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Lifetime: Time He/She Felt Most Suicidal	Past 1 month
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

<u>Lifetime</u> - ***Most Severe Ideation:*** _____ _____
Type # (1-5) ***Description of Ideation***

<u>Recent</u> - ***Most Severe Ideation:*** _____ _____
Type # (1-5) ***Description of Ideation***

	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 3 months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted or self-interrupted _____	**Yes** ☐ **No** ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of preparatory acts _____	**Yes** ☐ **No** ☐ Total # of preparatory acts _____

	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Attachment 6 Columbia-Suicide Severity Rating Scale (C-SSRS) "Since Last Visit"

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit - Clinical

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ **No** ☐

If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ **No** ☐

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ **No** ☐

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ **No** ☐

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ **No** ☐

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Frequency ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of preparatory acts _____
Suicide: Death by suicide occurred since last assessment.	**Yes** **No** ☐ ☐
	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Attachment 7 PROMIS Short Form Fatigue

Pediatric Fatigue - Short Form

Please respond to each item by marking one box per row.

In the past 7 days…….

	Never	Almost Never	Sometimes	Often	Almost Always
Being tired made it hard for me to play or go out with my friends as much as I'd like.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt weak.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I got tired easily.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Being tired made it hard for me to keep up with my schoolwork.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I had trouble finishing things because I was too tired.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I had trouble starting things because I was too tired.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was so tired it was hard for me to pay attention.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was too tired to do sports or exercise.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was too tired to do things outside.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was too tired to enjoy the things I like to do.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

During the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7 1	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3 2	I have trouble <u>starting</u> things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

FATEXP41 3	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40 4	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35 5	How much were you bothered by your fatigue on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49 6	To what degree did your fatigue interfere with your physical functioning?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATIMP3 7	How often did you have to push yourself to get things done because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP16 8	How often did you have trouble finishing things because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Attachment 8 BarTH Syndrome Symptom Assessment (BTHS-SA)

BarTH Syndrome Symptom Assessment (BTHS-SA) – Adolescent version

Instructions: The following questions ask about **Barth Syndrome**. Please select the response that best describes your experience with Barth Syndrome **over the past 24 hours.** Please select only one answer for each question. Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

Please indicate (with a check mark ☑) responses to the questions below.

1. Please rate your worst feeling of tiredness at rest in the past 24 hours.	No tiredness at all ☐	Mild tiredness ☐	Moderate tiredness ☐	Severe tiredness ☐	Very severe tiredness ☐
2. Please rate your worst feeling of tiredness during activities in the past 24 hours.	No tiredness at all ☐	Mild tiredness ☐	Moderate tiredness ☐	Severe tiredness ☐	Very severe tiredness ☐
3. Please rate your worst feeling of muscle weakness at rest in the past 24 hours.	No muscle weakness at all ☐	Mild muscle weakness ☐	Moderate muscle weakness ☐	Severe muscle weakness ☐	Very severe muscle weakness ☐
4. Please rate your worst feeling of muscle weakness during activities in the past 24 hours.	No muscle weakness at all ☐	Mild muscle weakness ☐	Moderate muscle weakness ☐	Severe muscle weakness ☐	Very severe muscle weakness ☐
5. Please rate your worst feeling of muscle pain at rest in the past 24 hours.	No muscle pain at all ☐	Mild muscle pain ☐	Moderate muscle pain ☐	Severe muscle pain ☐	Very severe muscle pain ☐
6. Please rate your worst feeling of muscle pain due to activities in the past 24 hours.	No muscle pain at all ☐	Mild muscle pain ☐	Moderate muscle pain ☐	Severe muscle pain ☐	Very severe muscle pain ☐
7. Please rate your worst feeling of early fullness when eating in the past 24 hours.	No feeling of early fullness at all ☐	Mild feeling of early fullness ☐	Moderate feeling of early fullness ☐	Severe feeling of early fullness ☐	Very severe feeling of early fullness ☐
8. Please rate your worst difficulty eating (for example, chewing and/or swallowing) in the past 24 hours.	No difficulty eating at all ☐	Mild difficulty eating ☐	Moderate difficulty eating ☐	Severe difficulty eating ☐	Very severe difficulty eating ☐
9. Please rate your worst feeling of headache in the past 24 hours.	No headache at all ☐	Mild headache ☐	Moderate headache ☐	Severe headache ☐	Very severe headache ☐

BarTH Syndrome Symptom Assessment (BTHS-SA) – Adult version

Instructions: The following questions ask about **Barth Syndrome**. Please select the response that best describes your experience with Barth Syndrome **over the past 24 hours.** Please select only one answer for each question. Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

Please indicate (with a check mark ☑) responses to the questions below.

1. Please rate your worst feeling of tiredness at rest in the past 24 hours.	No tiredness at all ☐	Mild tiredness ☐	Moderate tiredness ☐	Severe tiredness ☐	Very severe tiredness ☐
2. Please rate your worst feeling of tiredness during activities in the past 24 hours.	No tiredness at all ☐	Mild tiredness ☐	Moderate tiredness ☐	Severe tiredness ☐	Very severe tiredness ☐
3. Please rate your worst feeling of muscle weakness at rest in the past 24 hours.	No muscle weakness at all ☐	Mild muscle weakness ☐	Moderate muscle weakness ☐	Severe muscle weakness ☐	Very severe muscle weakness ☐
4. Please rate your worst feeling of muscle weakness during activities in the past 24 hours.	No muscle weakness at all ☐	Mild muscle weakness ☐	Moderate muscle weakness ☐	Severe muscle weakness ☐	Very severe muscle weakness ☐
5. Please rate your worst feeling of muscle pain at rest in the past 24 hours.	No muscle pain at all ☐	Mild muscle pain ☐	Moderate muscle pain ☐	Severe muscle pain ☐	Very severe muscle pain ☐
6. Please rate your worst feeling of muscle pain due to activities in the past 24 hours.	No muscle pain at all ☐	Mild muscle pain ☐	Moderate muscle pain ☐	Severe muscle pain ☐	Very severe muscle pain ☐
7. Please rate your worst feeling of dizziness/lightheadedness in the past 24 hours.	No dizziness/ lightheaded ness at all ☐	Mild dizziness/ lightheaded ness ☐	Moderate dizziness/ lightheaded ness ☐	Severe dizziness/ lightheaded ness ☐	Very severe dizziness/ lightheaded ness ☐
8. Please rate your worst feeling of shortness of breath in the past 24 hours.	No shortness of breath at all ☐	Mild shortness of breath ☐	Moderate shortness of breath ☐	Severe shortness of breath ☐	Very severe shortness of breath ☐

Attachment 9 Patient Global Impression (PGI) Scales

Patient Global Impression of Symptoms (Patient age 12-15)

Date Completed: _____

The following questions ask you about your Barth Syndrome symptoms OVER THE PAST WEEK.

1. How bad have your Barth Syndrome symptoms been over the past week?
   - ☐ No Symptoms
   - ☐ Mild Symptoms
   - ☐ Moderate Symptoms
   - ☐ Severe Symptoms
   - ☐ Very Severe Symptoms

2. How bad has your feeling of tiredness at rest been over the past week?
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

3. How bad has your feeling of tiredness during activities been over the past week?
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

4. How bad has your feeling of muscle weakness at rest been over the past week?
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness
   - ☐ Moderate Muscle Weakness
   - ☐ Severe Muscle Weakness
   - ☐ Very Severe Muscle Weakness

5. How bad has your feeling of muscle weakness during activities been over the past week?
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness
   - ☐ Moderate Muscle Weakness
   - ☐ Severe Muscle Weakness
   - ☐ Very Severe Muscle Weakness

6. How bad has your feeling of muscle pain at rest been over the past week?
   - ☐ No Muscle Pain
   - ☐ Mild Muscle Pain
   - ☐ Moderate Muscle Pain
   - ☐ Severe Muscle Pain
   - ☐ Very Severe Muscle Pain

7. How bad has your feeling of muscle pain due to activities been over the past week?
   - ☐ No Muscle Pain
   - ☐ Mild Muscle Pain
   - ☐ Moderate Muscle Pain
   - ☐ Severe Muscle Pain
   - ☐ Very Severe Muscle Pain

8. How bad has your feeling of early fullness when eating been over the past week?
   - ☐ No Early Fullness
   - ☐ Mild Early Fullness
   - ☐ Moderate Early Fullness
   - ☐ Severe Early Fullness
   - ☐ Very Severe Early Fullness

9. How bad has your feeling of difficulty eating (for example, chewing and/or swallowing) been over the past week?
   - ☐ No Difficulty Eating
   - ☐ Mild Difficulty Eating
   - ☐ Moderate Difficulty Eating
   - ☐ Severe Difficulty Eating
   - ☐ Very Severe Difficulty Eating

10. How bad has your feeling of headache been over the past week?
    - ☐ No Headache
    - ☐ Mild Headache
    - ☐ Moderate Headache
    - ☐ Severe Headache
    - ☐ Very Severe Headache

Patient Global Impression of Symptoms (Patient age >= 16)

Date Completed: _____

The following questions ask you about your Barth Syndrome symptoms OVER THE PAST WEEK.

1. How bad have your Barth Syndrome symptoms been over the past week?
   - ☐ No Symptoms
   - ☐ Mild Symptoms
   - ☐ Moderate Symptoms
   - ☐ Severe Symptoms
   - ☐ Very Severe Symptoms

2. How bad has your feeling of tiredness at rest been over the past week?
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

3. How bad has your feeling of tiredness during activities been over the past week?
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

4. How bad has your feeling of muscle weakness at rest been over the past week?
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness
   - ☐ Moderate Muscle Weakness
   - ☐ Severe Muscle Weakness
   - ☐ Very Severe Muscle Weakness

5. How bad has your feeling of muscle weakness during activities been over the past week?
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness
   - ☐ Moderate Muscle Weakness
   - ☐ Severe Muscle Weakness
   - ☐ Very Severe Muscle Weakness

6. How bad has your feeling of muscle pain at rest been over the past week?
   - ☐ No Muscle Pain
   - ☐ Mild Muscle Pain
   - ☐ Moderate Muscle Pain
   - ☐ Severe Muscle Pain
   - ☐ Very Severe Muscle Pain

7. How bad has your feeling of muscle pain due to activities been over the past week?
   - ☐ No Muscle Pain
   - ☐ Mild Muscle Pain
   - ☐ Moderate Muscle Pain
   - ☐ Severe Muscle Pain
   - ☐ Very Severe Muscle Pain

8. How bad has your feeling of dizziness/lightheadedness been over the past week?
   - ☐ No Dizziness/Lightheadedness
   - ☐ Mild Dizziness/Lightheadedness
   - ☐ Moderate Dizziness/Lightheadedness
   - ☐ Severe Dizziness/Lightheadedness
   - ☐ Very Severe Dizziness/Lightheadedness

9. How bad has your feeling of shortness of breath been over the past week?
   - ☐ No Shortness of Breath
   - ☐ Mild Shortness of Breath
   - ☐ Moderate Shortness of Breath
   - ☐ Severe Shortness of Breath
   - ☐ Very Severe Shortness of Breath

Patient Global Impression of Change (Patient age 12-15)

To be administered at Week 12 of Treatment Period 1.

Date Completed: _____

Please think about how your Barth Syndrome symptoms have changed from the time just before you started the study medication in Treatment Period 1 to today. The following questions ask you about how your symptoms have changed SINCE THE TIME JUST BEFORE YOU STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 1 TO TODAY.

1. Please choose the response below that best describes how your Barth Syndrome symptoms have changed since the time just before you started the study medication in Treatment Period 1 to today. My Barth Syndrome symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes how your feeling of tiredness at rest has changed since the time just before you started the study medication in Treatment Period 1 to today. My tiredness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

3. Please choose the response below that best describes how your feeling of tiredness during activities has changed since the time just before you started the study medication in Treatment Period 1 to today. My tiredness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

4. Please choose the response below that best describes how your feeling of muscle weakness at rest has changed since the time just before you started the study medication in Treatment Period 1 to today. My muscle weakness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

5. Please choose the response below that best describes how your feeling of muscle weakness during activities has changed since the time just before you started the study medication in Treatment Period 1 to today. My muscle weakness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

6. Please choose the response below that best describes how your feeling of muscle pain at rest has changed since the time just before you started the study medication in Treatment Period 1 to today. My muscle pain at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

7. Please choose the response below that best describes how your feeling of muscle pain during activities has changed since the time just before you started the study medication in Treatment Period 1 to today. My muscle pain during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

8. Please choose the response below that best describes how your feeling of early fullness when eating has changed since the time just before you started the study medication in Treatment Period 1 to today. My feeling of early fullness when eating is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

9. Please choose the response below that best describes how your feeling of difficulty eating (for example, chewing and/or swallowing) has changed since the time just before you started the study medication in Treatment Period 1 to today. My feeling of difficulty eating is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

10. Please choose the response below that best describes how your feeling of headache has changed since the time just before you started the study medication in Treatment Period 1 to today. My feeling of headache is:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

Patient Global Impression of Change (Patient age >= 16)

To be administered at Week 12 of Treatment Period 1.

Date Completed: _____

Please think about how your Barth Syndrome symptoms have changed from the time just before you started the study medication in Treatment Period 1 to today. The following questions ask you about how your symptoms have changed SINCE THE TIME JUST BEFORE YOU STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 1 TO TODAY.

1. Please choose the response below that best describes how your Barth Syndrome symptoms have changed since the time just before you started the study medication in Treatment Period 1 to today. My Barth Syndrome symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes how your feeling of tiredness at rest has changed since the time just before you started the study medication in Treatment Period 1 to today. My tiredness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

3. Please choose the response below that best describes how your feeling of tiredness during activities has changed since the time just before you started the study medication in Treatment Period 1 to today. My tiredness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

4. Please choose the response below that best describes how your feeling of muscle weakness at rest has changed since the time just before you started the study medication in Treatment Period 1 to today. My muscle weakness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

5. Please choose the response below that best describes how your feeling of muscle weakness during activities has changed since the time just before you started the study medication in Treatment Period 1 to today. My muscle weakness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

6. Please choose the response below that best describes how your feeling of muscle pain at rest has changed since the time just before you started the study medication in Treatment Period 1 to today. My muscle pain at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

7. Please choose the response below that best describes how your feeling of muscle pain during activities has changed since the time just before you started the study medication in Treatment Period 1 to today. My muscle pain during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

8. Please choose the response below that best describes how your feeling of dizziness/lightheadedness has changed since the time just before you started the study medication in Treatment Period 1 to today. My feeling of dizziness/lightheadedness is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

9. Please choose the response below that best describes how your feeling of shortness of breath has changed since the time just before you started the study medication in Treatment Period 1 to today. My feeling of shortness of breath is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

Patient Global Impression of Change (Patient age 12-15)

To be administered at Week 12 of Treatment Period 2.

Date Completed: _____

Please think about how your Barth Syndrome symptoms have changed from the time just before you started the study medication in Treatment Period 2 to today. The following questions ask you about how your symptoms have changed SINCE THE TIME JUST BEFORE YOU STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 2 TO TODAY.

1. Please choose the response below that best describes how your Barth Syndrome symptoms have changed since the time just before you started the study medication in Treatment Period 2 to today. My Barth Syndrome symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes how your feeling of tiredness at rest has changed since the time just before you started the study medication in Treatment Period 2 to today. My tiredness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

3. Please choose the response below that best describes how your feeling of tiredness during activities has changed since the time just before you started the study medication in Treatment Period 2 to today. My tiredness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

4. Please choose the response below that best describes how your feeling of muscle weakness at rest has changed since the time just before you started the study medication in Treatment Period 2 to today. My muscle weakness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

5. Please choose the response below that best describes how your feeling of muscle weakness during activities has changed since the time just before you started the study medication in Treatment Period 2 to today. My muscle weakness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

6. Please choose the response below that best describes how your feeling of muscle pain at rest has changed since the time just before you started the study medication in Treatment Period 2 to today. My muscle pain at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

7. Please choose the response below that best describes how your feeling of muscle pain during activities has changed since the time just before you started the study medication in Treatment Period 2 to today. My muscle pain during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

8. Please choose the response below that best describes how your feeling of <u>early fullness when eating</u> has changed since the time just before you started the study medication in Treatment Period 2 to today. My feeling of early fullness when eating is:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

9. Please choose the response below that best describes how your feeling of <u>difficulty eating (for example, chewing and/or swallowing)</u> has changed since the time just before you started the study medication in Treatment Period 2 to today. My feeling of difficulty eating is:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

10. Please choose the response below that best describes how your feeling of <u>headache</u> has changed since the time just before you started the study medication in Treatment Period 2 to today. My feeling of headache is:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

Patient Global Impression of Change (Patient age >= 16)

To be administered at Week 12 of Treatment Period 2.

Date Completed: _____

Please think about how your Barth Syndrome symptoms have changed from the time just before you started the study medication in Treatment Period 2 to today. The following questions ask you about how your symptoms have changed SINCE THE TIME JUST BEFORE YOU STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 2 TO TODAY.

1. Please choose the response below that best describes how your Barth Syndrome symptoms have changed since the time just before you started the study medication in Treatment Period 2 to today. My Barth Syndrome symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes how your feeling of tiredness at rest has changed since the time just before you started the study medication in Treatment Period 2 to today. My tiredness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

3. Please choose the response below that best describes how your feeling of tiredness during activities has changed since the time just before you started the study medication in Treatment Period 2 to today. My tiredness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

4. Please choose the response below that best describes how your feeling of muscle weakness at rest has changed since the time just before you started the study medication in Treatment Period 2 to today. My muscle weakness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

5. Please choose the response below that best describes how your feeling of muscle weakness during activities has changed since the time just before you started the study medication in Treatment Period 2 to today. My muscle weakness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

6. Please choose the response below that best describes how your feeling of muscle pain at rest has changed since the time just before you started the study medication in Treatment Period 2 to today. My muscle pain at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

7. Please choose the response below that best describes how your feeling of muscle pain during activities has changed since the time just before you started the study medication in Treatment Period 2 to today. My muscle pain during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

8. Please choose the response below that best describes how your feeling of dizziness/lightheadedness has changed since the time just before you started the study medication in Treatment Period 2 to today. My feeling of dizziness/lightheadedness is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

9. Please choose the response below that best describes how your feeling of shortness of breath has changed since the time just before you started the study medication in Treatment Period 2 to today. My feeling of shortness of breath is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

Attachment 10 Clinician Global Impression (CGI) Scales

Clinician Global Impression of Symptoms (all ages)

Date Completed: _____

1. Overall, how severe are the patient's Barth Syndrome symptoms today?
   - ☐ No Symptoms
   - ☐ Mild Symptoms
   - ☐ Moderate Symptoms
   - ☐ Severe Symptoms
   - ☐ Very Severe Symptoms

Clinician Global Impression of Change (All ages)

To be administered at Week 12 of Treatment Period 1.

Date Completed: _____

Please think about how the patient's Barth Syndrome symptoms have changed from the time just before he/she started the study medication in Treatment Period 1 to today. The following questions ask you about how the patient's symptoms have changed SINCE THE TIME JUST BEFORE HE/SHE STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 1 TO TODAY.

1. Please choose the response below that best describes how the patient's Barth Syndrome symptoms have changed since the time just before he/she started the study medication in Treatment Period 1 to today. The patient's Barth Syndrome symptoms are:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

Clinician Global Impression of Change (All ages)

To be administered at Week 12 of Treatment Period 2.

Date Completed: _____

Please think about how the patient's Barth Syndrome symptoms have changed from the time just before he/she started the study medication in Treatment Period 2 to today. The following questions ask you about how the patient's symptoms have changed SINCE THE TIME JUST BEFORE HE/SHE STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 2 TO TODAY.

1. Please choose the response below that best describes how the patient's Barth Syndrome symptoms have changed since the time just before he/she started the study medication in Treatment Period 2 to today. The patient's Barth Syndrome symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

Attachment 11 Caregiver Global Impression (CaGI) Scales

Caregiver Global Impression of Symptoms (Patient age 12-15)

Date Completed: _____

The following questions ask you about your child's Barth Syndrome symptoms OVER THE PAST WEEK. Please base your responses on what you have observed or what your child has told you about their symptoms in the past week.

1. How bad have your child's Barth Syndrome symptoms been over the past week?
   - ☐ No Symptoms
   - ☐ Mild Symptoms
   - ☐ Moderate Symptoms
   - ☐ Severe Symptoms
   - ☐ Very Severe Symptoms

2. How bad has your child's feeling of tiredness at rest been over the past week?
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

3. How bad has your child's feeling of tiredness during activities been over the past week?
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

4. How bad has your child's feeling of muscle weakness at rest been over the past week?
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness
   - ☐ Moderate Muscle Weakness
   - ☐ Severe Muscle Weakness
   - ☐ Very Severe Muscle Weakness

5. How bad has your child's feeling of muscle weakness during activities been over the past week?
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness
   - ☐ Moderate Muscle Weakness
   - ☐ Severe Muscle Weakness

- ☐ Very Severe Muscle Weakness

6. How bad has your child's feeling of <u>muscle pain at rest</u> been over the past week?
   - ☐ No Muscle Pain
   - ☐ Mild Muscle Pain
   - ☐ Moderate Muscle Pain
   - ☐ Severe Muscle Pain
   - ☐ Very Severe Muscle Pain

7. How bad has your child's feeling of <u>muscle pain due to activities</u> been over the past week?
   - ☐ No Muscle Pain
   - ☐ Mild Muscle Pain
   - ☐ Moderate Muscle Pain
   - ☐ Severe Muscle Pain
   - ☐ Very Severe Muscle Pain

8. How bad has your child's feeling of <u>early fullness when eating</u> been over the past week?
   - ☐ No Early Fullness
   - ☐ Mild Early Fullness
   - ☐ Moderate Early Fullness
   - ☐ Severe Early Fullness
   - ☐ Very Severe Early Fullness

9. How bad has your child's feeling of <u>difficulty eating (for example, chewing and/or swallowing)</u> been over the past week?
   - ☐ No Difficulty Eating
   - ☐ Mild Difficulty Eating
   - ☐ Moderate Difficulty Eating
   - ☐ Severe Difficulty Eating
   - ☐ Very Severe Difficulty Eating

10. How bad has your child's feeling of <u>headache</u> been over the past week?
    - ☐ No Headache
    - ☐ Mild Headache
    - ☐ Moderate Headache
    - ☐ Severe Headache
    - ☐ Very Severe Headache

Caregiver Global Impression of Symptoms (Patient age >= 16)

Date Completed: _____

The following questions ask you about the individual with Barth Syndrome that you care for and the symptoms that he/she has had OVER THE PAST WEEK. Please base your responses on what you have observed or what the individual with Barth Syndrome has told you about his/her symptoms in the past week.

1. How bad have his/her Barth Syndrome symptoms been over the past week?
   - ☐ No Symptoms
   - ☐ Mild Symptoms
   - ☐ Moderate Symptoms
   - ☐ Severe Symptoms
   - ☐ Very Severe Symptoms

2. How bad has his/her feeling of tiredness at rest been over the past week?
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

3. How bad has his/her feeling of tiredness during activities been over the past week?
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

4. How bad has his/her feeling of muscle weakness at rest been over the past week?
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness
   - ☐ Moderate Muscle Weakness
   - ☐ Severe Muscle Weakness
   - ☐ Very Severe Muscle Weakness

5. How bad has his/her feeling of muscle weakness during activities been over the past week?
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness
   - ☐ Moderate Muscle Weakness
   - ☐ Severe Muscle Weakness

- ☐ Very Severe Muscle Weakness

6. How bad has his/her feeling of <u>muscle pain at rest</u> been over the past week?
   - ☐ No Muscle Pain
   - ☐ Mild Muscle Pain
   - ☐ Moderate Muscle Pain
   - ☐ Severe Muscle Pain
   - ☐ Very Severe Muscle Pain

7. How bad has his/her feeling of <u>muscle pain due to activities</u> been over the past week?
   - ☐ No Muscle Pain
   - ☐ Mild Muscle Pain
   - ☐ Moderate Muscle Pain
   - ☐ Severe Muscle Pain
   - ☐ Very Severe Muscle Pain

8. How bad has his/her feeling of <u>dizziness/lightheadedness</u> been over the past week?
   - ☐ No Dizziness/Lightheadedness
   - ☐ Mild Dizziness/Lightheadedness
   - ☐ Moderate Dizziness/Lightheadedness
   - ☐ Severe Dizziness/Lightheadedness
   - ☐ Very Severe Dizziness/Lightheadedness

9. How bad has his/her feeling of <u>shortness of breath</u> been over the past week?
   - ☐ No Shortness of Breath
   - ☐ Mild Shortness of Breath
   - ☐ Moderate Shortness of Breath
   - ☐ Severe Shortness of Breath
   - ☐ Very Severe Shortness of Breath

Caregiver Global Impression of Change (Patient age 12-15)

To be administered at Week 12 of Treatment Period 1.

Date Completed: _____

Please think about how your child's Barth Syndrome symptoms have changed from the time just before he/she started the study medication in Treatment Period 1 to today. The following questions ask you about how your child's symptoms have changed SINCE THE TIME JUST BEFORE HE/SHE STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 1 TO TODAY. Please base your responses on what you have observed or what your child has told you about their symptoms.

1. Please choose the response below that best describes how your child's Barth Syndrome symptoms have changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's Barth Syndrome symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes how your child's feeling of tiredness at rest has changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's tiredness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

3. Please choose the response below that best describes how your child's feeling of tiredness during activities has changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's tiredness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse

- ☐ Moderately Worse
- ☐ Very much Worse

4. Please choose the response below that best describes how your child's feeling of <u>muscle weakness at rest</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's muscle weakness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

5. Please choose the response below that best describes how your child's feeling of <u>muscle weakness during activities</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's muscle weakness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

6. Please choose the response below that best describes how your child's feeling of <u>muscle pain at rest</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's muscle pain at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

7. Please choose the response below that best describes how your child's feeling of <u>muscle pain during activities</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's muscle pain during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better

- ☐ No Change
- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Very much Worse

8. Please choose the response below that best describes how your child's feeling of <u>early fullness when eating</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's feeling of early fullness when eating is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

9. Please choose the response below that best describes how your child's feeling of <u>difficulty eating (for example, chewing and/or swallowing)</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's feeling of difficulty eating is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

10. Please choose the response below that best describes how your child's feeling of <u>headache</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. My child's feeling of headache is:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

Caregiver Global Impression of Change (Patient age >= 16)

To be administered at Week 12 of Treatment Period 1.

Date Completed: _____

Please think about the individual that you care for and how his/her Barth Syndrome symptoms have changed from the time just before he/she started the study medication in Treatment Period 1 to today. The following questions ask you about how his/her symptoms have changed SINCE THE TIME JUST BEFORE HE/SHE STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 1 TO TODAY. Please base your responses on what you have observed or what the individual with Barth Syndrome has told you about his/her symptoms.

1. Please choose the response below that best describes how his/her Barth Syndrome symptoms have changed since the time just before he/she started the study medication in Treatment Period 1 to today. His/her Barth Syndrome symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes how his/her feeling of tiredness at rest has changed since the time just before he/she started the study medication in Treatment Period 1 to today. His/her tiredness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

3. Please choose the response below that best describes how his/her feeling of tiredness during activities has changed since the time just before he/she started the study medication in Treatment Period 1 to today. His/her tiredness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse

- ☐ Moderately Worse
- ☐ Very much Worse

4. Please choose the response below that best describes how his/her feeling of <u>muscle weakness at rest</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. His/her muscle weakness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

5. Please choose the response below that best describes how his/her feeling of <u>muscle weakness during activities</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. His/her muscle weakness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

6. Please choose the response below that best describes how his/her feeling of <u>muscle pain at rest</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. His/her muscle pain at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

7. Please choose the response below that best describes how his/her feeling of <u>muscle pain during activities</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. His/her muscle pain during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change

- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Very much Worse

8. Please choose the response below that best describes how his/her feeling of <u>dizziness/lightheadedness</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. His/her dizziness/lightheadedness is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

9. Please choose the response below that best describes how his/her feeling of <u>shortness of breath</u> has changed since the time just before he/she started the study medication in Treatment Period 1 to today. His/her feeling of shortness of breath is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

Caregiver Global Impression of Change (Patient age 12-15)

To be administered at Week 12 of Treatment Period 2.

Date Completed: _____

Please think about how your child's Barth Syndrome symptoms have changed from the time just before he/she started the study medication in Treatment Period 2 to today. The following questions ask you about how your child's symptoms have changed SINCE THE TIME JUST BEFORE HE/SHE STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 2 TO TODAY. Please base your responses on what you have observed or what your child has told you about their symptoms.

1. Please choose the response below that best describes how your child's Barth Syndrome symptoms have changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's Barth Syndrome symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes how your child's feeling of tiredness at rest has changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's tiredness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

3. Please choose the response below that best describes how your child's feeling of tiredness during activities has changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's tiredness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse

- ☐ Moderately Worse
- ☐ Very much Worse

4. Please choose the response below that best describes how your child's feeling of <u>muscle weakness at rest</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's muscle weakness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

5. Please choose the response below that best describes how your child's feeling of <u>muscle weakness during activities</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's muscle weakness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

6. Please choose the response below that best describes how your child's feeling of <u>muscle pain at rest</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's muscle pain at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

7. Please choose the response below that best describes how your child's feeling of <u>muscle pain during activities</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's muscle pain during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better

- ☐ No Change
- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Very much Worse

8. Please choose the response below that best describes how your child's feeling of <u>early fullness when eating</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's feeling of early fullness when eating is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

9. Please choose the response below that best describes how your child's feeling of <u>difficulty eating (for example, chewing and/or swallowing)</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's feeling of difficulty eating is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

10. Please choose the response below that best describes how your child's feeling of <u>headache</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. My child's feeling of headache is:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

Caregiver Global Impression of Change (Patient age >= 16)

To be administered at Week 12 of Treatment Period 2.

Date Completed: _____

Please think about the individual that you care for and how his/her Barth Syndrome symptoms have changed from the time just before he/she started the study medication in Treatment Period 2 to today. The following questions ask you about how his/her symptoms have changed SINCE THE TIME JUST BEFORE HE/SHE STARTED THE STUDY MEDICATION IN TREATMENT PERIOD 2 TO TODAY. Please base your responses on what you have observed or what the individual with Barth Syndrome has told you about his/her symptoms.

1. Please choose the response below that best describes how his/her Barth Syndrome symptoms have changed since the time just before he/she started the study medication in Treatment Period 2 to today. His/her Barth Syndrome symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes how his/her feeling of tiredness at rest has changed since the time just before he/she started the study medication in Treatment Period 2 to today. His/her tiredness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

3. Please choose the response below that best describes how his/her feeling of tiredness during activities has changed since the time just before he/she started the study medication in Treatment Period 2 to today. His/her tiredness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse

- ☐ Moderately Worse
- ☐ Very much Worse

4. Please choose the response below that best describes how his/her feeling of <u>muscle weakness at rest</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. His/her muscle weakness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

5. Please choose the response below that best describes how his/her feeling of <u>muscle weakness during activities</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. His/her muscle weakness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

6. Please choose the response below that best describes how his/her feeling of <u>muscle pain at rest</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. His/her muscle pain at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

7. Please choose the response below that best describes how his/her feeling of <u>muscle pain during activities</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. His/her muscle pain during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change

- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Very much Worse

8. Please choose the response below that best describes how his/her feeling of <u>dizziness/lightheadedness</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. His/her dizziness/lightheadedness is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

9. Please choose the response below that best describes how his/her feeling of <u>shortness of breath</u> has changed since the time just before he/she started the study medication in Treatment Period 2 to today. His/her feeling of shortness of breath is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

Attachment 12 EQ-5D

Health Questionnaire

English version for the USA

EQ-5D-Y

Describing your health TODAY

Please check the ONE box that best describes your health TODAY.

Mobility *(walking around)*

I have no problems walking around ❑

I have some problems walking around ❑

I have a lot of problems walking around ❑

Taking care of myself

I have no problems taking a bath or shower by myself or getting dressed by myself ❑

I have some problems taking a bath or shower by myself or getting dressed by myself ❑

I have a lot of problems taking a bath or shower by myself or getting dressed by myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad, or unhappy

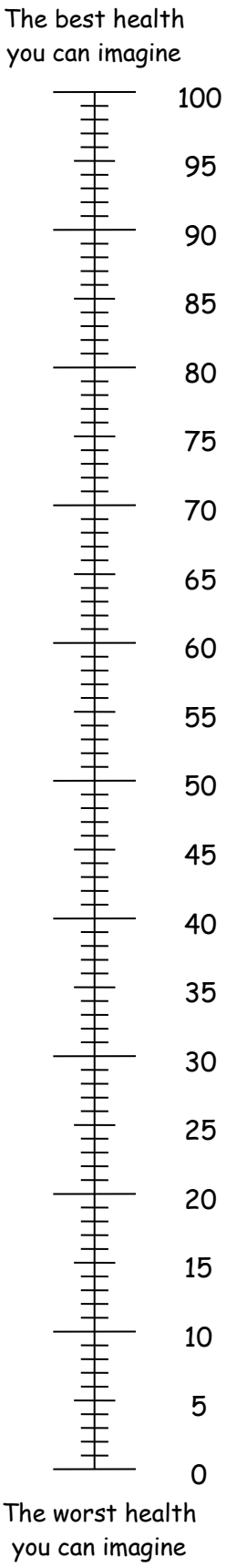
I am not worried, sad, or unhappy ❑

I am a little worried, sad, or unhappy ❑

I am very worried, sad, or unhappy ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the line to show how good or bad your health is TODAY.



Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

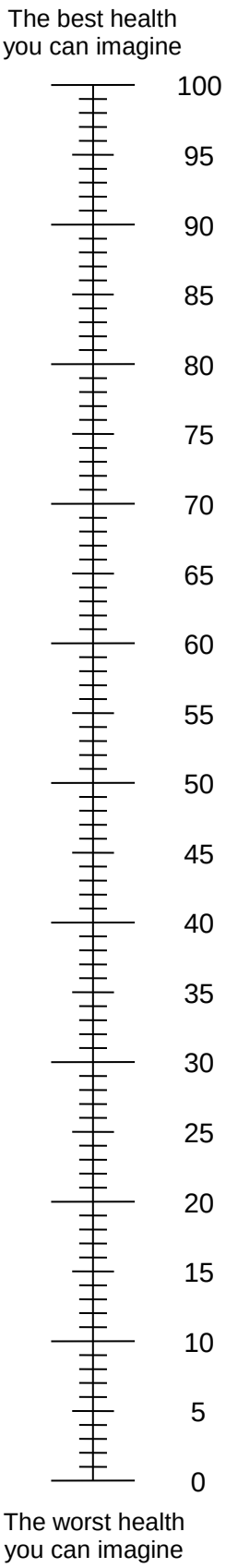
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Attachment 13 SWAY Application Balance Assessments

1. Access the portal via either:
    a. Computer: login to my.swaybalance.com utilizing email address and password.
    b. iPhone: Ensure the application is downloaded on the iPhone (app can be located in the Sway Balance app in the app store)
2. Enter patient profile. Information required:
    a. First name: site number
    b. Last name: subject number
    c. Height: in feet/inches.
    d. Weight: in lbs.
    e. Birth date:
    f. Gender:
    g. Group: SPIBA-201
    h. Protocol: Sports
3. Prior to providing subject the phone, ensure the phone is in airplane mode (to ensure testing is not disrupted), with WiFi enabled (if possible, to allow automatic syncing to portal). Ensure case is removed from phone.
4. At the Screening visit: Choose Baseline (as opposed to create event). At subsequent visits, choose Create Event.
5. Ask the subject to follow the screen's directions on 10 second stand positions, during test intervals.
   "During testing, please hold the phone with both hands against your chest (region of sternum). *The phone will make a sound to let you know a section of the test has been completed."* (Screen of phone will be against sternum of subject)
    a. Stand with feet together with eyes closed.
    b. Stand in tandem stance with right foot in front with eyes closed.
    c. Stand in tandem stance with left foot in front with eyes closed.
    d. Stand on right leg with **EYES OPEN**
    e. Stand on left leg with **EYES OPEN**
    f. 5 motion reaction tests

At the Screening Visit: Have subject complete at least 2 additional trials following 1st trial

At subsequent visits, subject will only complete 1 trial.

Attachment 14 6-Minute Walk Test (6MWT)

Performed based on American Thoracic Society Guidelines for the 6-Minute Walk Test (March 2002). To be completed following strength testing.

1. Testing Guidelines
    a. 10 minute rest period will be given prior to the test
    b. Subjects should wear comfortable clothes and appropriate shoes for walking
    c. Subject may not touch the wall while walking

2. Set up
    a. Test will be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface. The walking course will be 30 m (100 feet) in length.
    b. Turn around points will be marked with a cone. A starting line (to mark the beginning and end of each 60-m lap) will be marked on the floor using brightly colored tape.
    c. Area will be within easy access of medical assistance.
    d. One lap is the distance from one cone to the other and back (60 meters)

3. Conducting the Test
    a. Subject will sit in a chair for 10 minutes. During this time tester should obtain the following baseline measurements: heart rate, blood pressure and SPO2.
    b. Following the 10 minute rest period, subject will stand and tester will obtain baseline dyspnea and fatigue utilizing the Borg Scale using the following statements:
        i. "Please grade your level of shortness of breath using this scale."
        ii. "Please grade your level of fatigue using this scale."
    c. Tester will assemble stopwatch, timer, clipboard, Borg Scale and worksheet and move to starting point with subject.
    d. Tester will give the subject the following instruction regarding the test:
        i. *"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."*
    e. Tester will then demonstrate walking one lap and turning around the cone briskly.
    f. Next tester will state:
        i. *"Are you ready to do that? I will keep track of the number of laps you complete. Remember that the object is to walk as far as possible for 6 minutes, don't run or jog."*
    g. Tester will start timer as soon as subject starts to walk.
    h. Tester should remain 1-2 meters behind the start line with the stopwatch, worksheet, timing the test.
    i. Tester should not talk to anyone during the walk, use an even tone of voice when using the standard phrases of encouragement.

j. Tester will place a line on the worksheet each time subject returns to starting line.
k. If the subject stops during the walking test and needs a rest tester should say:
   i. *"You can lean against the wall if you would like; then continue to walk whenever you feel able."*
   ii. Do not stop the timer. If the subject stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), bring the chair over to the subject to sit on, discontinue the walk, note on the worksheet the distance, time stopped and reason for stopping prematurely.
l. After the first minute, tester should tell the subject the following (in even tones):
   i. *"You are doing well. You have 5 minutes to go."*
m. After the second minute, tester should tell the subject:
   i. *"Keep up the good work. You have 4 minutes to go."*
n. After 3 minutes, tester should tell the subject:
   i. *"You are doing well. You are halfway done."*
o. After 4 minutes, tester should tell the subject:
   i. *"Keep up the good work. You have only 2 minutes left."*
p. After 5 minutes, tester should tell the subject:
   i. *"You are doing well. You have only 1 minute to go."*
q. When the timer is 15 seconds from completion tester should say:
   i. *"In a moment I am going to tell you to stop. When I do, just stop right where you are and I will come to you."*
r. When the 6 minutes is up the tester should say:
   i. *"Stop!"*
   ii. Tester should walk to the subject (consider bringing chair if they look exhausted). Mark spot subject stopped with tape.
s. Tester should record Dyspnea using Borg scale.
   i. *Remind subject of breathing number that they chose before the exercise and ask the subject to grade their breathing level again (please grade your level of shortness of breath using this scale).*
t. Tester should record Fatigue using the Borg Scale.
   i. *Remind subject of fatigue number that they chose before the exercise and ask the subject to grade their breathing level again (please grade your level of fatigue using this scale).*
u. Tester should record heart rate and SPO2 using pulse oximeter.
v. Tester should ask subject:
   i. *"What, if anything, kept you from walking farther?"*
w. Tester should record number of laps based on number of tick marks on worksheet.
x. Tester should record additional distance covered (the number of meters in the final partial lap) using distance wheel. Calculate the total distance covered, rounding to the nearest meter and record it on the worksheet.
y. Congratulate the subject on good effort and offer a drink of water.

Attachment 15 Five Times Sit-to-Stand Test (5XSST)

Description:

Assesses functional lower extremity strength, transitional movements, balance, and fall risk.

Equipment:

Stopwatch; standard height chair with straight back (16 inches high).

Therapist Instructions:

Have the subject sit with their back against the back of the chair. Count each stand aloud so that the subject remains oriented. Stop the test when the subject achieves the standing position on the 5th repetition.

Subject Instructions:

“Please stand up straight as quickly as you can 5 times, without stopping in between. Keep your arms folded across your chest. I’ll be timing you with a stopwatch. Ready, begin.”

Attachment 16 Table for Grading the Severity of Site Reactions to Injections

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling	Same as for **Injection Site Erythema or Redness**	Same as for **Injection Site Erythema or Redness**	Same as for **Injection Site Erythema or Redness**	Same as for **Injection Site Erythema or Redness**
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

Adapted from Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2, November 2014.

Attachment 17 Sample Telephone Call (or other forms of communication) Script

This page provides a sample script for the phone call (or other forms of communication) that will be made to the subject occur approximately every 12 weeks (after the Part 2 Week 12 Visit) between clinical site visits after the subject is enrolled in Part 2 to ensure the safe and compliant use of the study drug and to appropriately collect the safety events with use of the study drug.

The sample script below is provided to assist clinical sites with conducting safety telephone calls (or other forms of communication). Additional questions are permitted to ensure completeness of answers.

During each safety telephone call (or other forms of communication), the following script should be followed:

Script

Hello, my name is _____, and I'm calling from (name of facility and/or Investigator's name office). I am calling since it has been about 3 months since we last spoke about your experience using elamipretide, the study drug in the Part 2 of the trial that you are involved in. May I ask you a few questions about your experience?

Have you or a trained caregiver been administering the study drug daily?

How many days since (our last telephone call or your last site visit) have you missed administering the study drug?

Do you have any questions/concerns regarding administering the study drug?

Have you experienced any worsening of your health or any new problems/conditions while on the study drug since (our last telephone call or your last site visit)?

Have you started or changed any medications since (our last telephone call or your last site visit)?

Could we schedule the next (telephone call or site visit)? (schedule telephone call or site visit)

Do you have any additional questions?

Thank you for speaking with me today. If you have any additional questions, please call me at (phone number).

01010-4.00 SPIBA-201 v4.0 a Phase 2 Placebo Crossover Trial with OLE to Evaluate Safety and Efficacy of Elamipretide SC in Barth Syndrome

Closed

19MAR2018
18:18 UTC

19MAR2018
19:05 UTC